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FOCAL CEREBRAL AND CEREBELLAR ATROPHY IN A HUMAN SUBJECT DUE TO ORGANIC MERCURY COMPOUNDS

BY

DONALD HUNTER and DOROTHY S. RUSSELL

From the Department for Research in Industrial Medicine (M.R.C.), and the Bernhard Baron Institute of Pathology, the London Hospital

Before the second world war a group of four patients suffering from profound neurological disturbances as a result of industrial exposure to methyl mercury compounds was studied by one of us. At the same time the effects of these compounds upon experimental rats and one monkey were assessed. A full account of this clinical and experimental work has been published (Hunter, Bomford, and Russell, 1940).

After an interval of 15 years one of these men (Case 4) has come to necropsy. Because it has afforded the first opportunity for a detailed histological study in this form of intoxication, and because the neuropathological changes proved both unexpected and intrinsically of considerable interest, we consider the case worthy of record.

Clinical

Recapitulation of Neurological Disturbance.—The subject, a man aged 23 when he first came under observation, had been exposed to dusts of methyl mercury phosphate and nitrate for a period of four months, beginning five months before admission to hospital. He had a squint and stuttered, both since childhood.

About April 13, 1937, he noticed numbness of his hands and forearms up to the elbow ; also of his lips and of the centre of the tip of his tongue. When examined by Dr. S. P. Meadows a week later there was slight impairment of two-point discrimination (at 0·5 cm.) at the tips of his fingers. Apart from a concomitant convergent squint no further objective neurological signs were found ; there was " no marked defect " in the visual fields (perimetry). Two days later (April 22) he spoke of having " pins and needles " in his hands, but said that this was improving. Dr. Meadows recorded a full neurological examination in which, again, impairment of two-point discrimination in the hands and fingers was alone found. Slight dysarthria was attributed to loss of all his teeth seven weeks previously.

After admission to The London Hospital (May 1) he was seen again by Dr. Meadows (May 3) who wrote : " Since I saw this patient 11 days ago there has been a remarkable change in him." There was now a marked concentric constriction of the visual fields (see Fig. 5 of 1940 report). His speech had deteriorated and was stammering, and he was slightly deaf. Gait was unsteady, his hands shaky, and he had difficulty with buttons, though subjectively the numbness had gone. His tongue and lips, however, still felt numb. Objective neurological findings were : moderate bilateral ptosis ; irregular fine nystagmus on deviation to right, left, and upwards ; marked incoordination of movements in the upper limbs, without wasting or weakness, becoming worse with the eyes shut ; difficulty in performing fine movements and rapid alternating movements ; slight wandering of the fingers with the hands outstretched, and a tendency for the hands to drop with eyes shut. In the lower limbs there was no wasting or weakness ; tone normal ; incoordination and gross dysmetria, however, were obvious. Reflexes were brisk and equal in all limbs ; diminished in the abdomen ; both plantar reflexes were extensor. Response to cotton-wool, pin-prick, and vibration was everywhere normal ; postural sensation was greatly impaired in the fingers, and slightly in the toes but not lost in the lips ; stereognosis was impaired in the hands ; two-point discrimination (at 1 cm.) was impaired at finger-tips. The patient showed marked ataxia with unsteady stance, overbalancing if the eyes were shut but just able to walk alone.

The further stages in this man's illness during his year's stay in hospital have already been fully recorded. It may be added that little change took place in his neurological state. Tremor was never observed. His ataxia remained gross and, when discharged a year later, he was quite helpless. He continued to attend the out-patient department for speech-therapy and physiotherapy and, in September, 1948, was readmitted to the wards for a month for reassessment. He was then found to be well orientated, his memory being good but dysphasia was gross. He had become blind in the left eye, the right showing severe constriction of the visual field as before. Nystagmus and bilateral ptosis persisted. The limbs when examined were affected as before. He was thus still grossly ataxic, helpless, unable to stand unaided or to walk without support. Attempts to feed himself proved " a long and messy undertaking ". His blood pressure was 180/130 mm. Hg.

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He was again admitted in September, 1950, being described then as intelligent, alert, and cooperative. His condition otherwise was unchanged. Blood pressure was 190/135 mm. Hg. Renal function tests gave normal results. He was finally admitted to Whipps Cross Hospital on December 14, 1952, with pneumonia and died there 14 days later.

Necropsy

An examination was made 22 hours after death by Dr. Keith Simpson, whose report is summarized as heart failure, myocardial fibrosis, and coronary atheroma. Back pressure congestion of liver, spleen, and kidneys; extensive ischaemic fibrosis of left ventricle of heart; no recent thrombus in atheromatous coronary arteries; chronic bronchitis with residual pneumonitis in lower half of lower lobe of left lung; emphysema of remainder of lungs, with infarcts in right upper lobe, and one at base of right lung. The remaining organs were of normal appearance. (Brain and spinal cord reserved.)

Histological Examination

The material received for examination included the brain, spinal cord, and portions of the sciatic and ulnar nerves, kidney, spleen, and a piece of heart muscle (left ventricle). All had been fixed in formaldehyde.

Macroscopic Examination of the Brain.—The leptomeninges appeared normal. The main cerebral arteries contained a few flecks of atheroma becoming confluent, but without stenosis, in the right vertebral artery. There was slight symmetrical convolutional atrophy at the frontal poles and severe about both calcarine fissures. The left optic nerve had been divided at the chiasm; the right appeared slightly flattened (measuring 0·6 by 0·2 cm.) but its cut surfaces appeared normal.

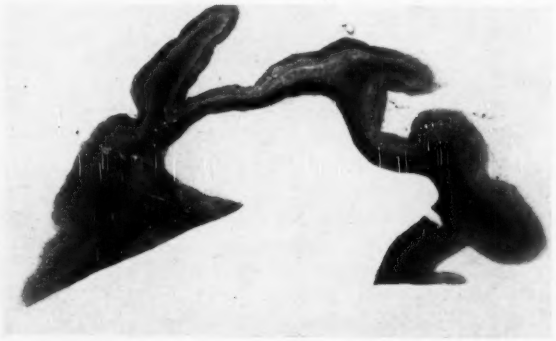


FIG. 1.—Coronal section of anterior part of left area striata to show gross atrophy. Weil-Davenport. × 2 (approx.).

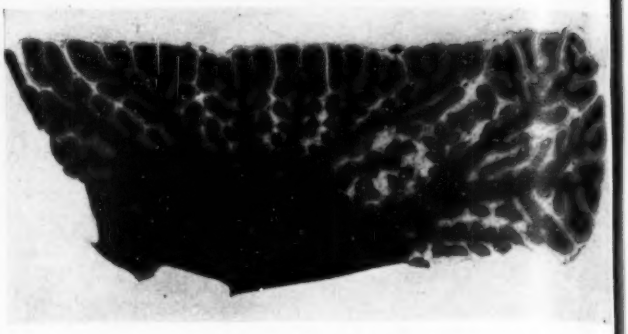


FIG. 2.—Lateral lobe of cerebellum. Note atrophy of folia in depths of sulci (right) with preservation of cortex at surface. Loyez' haematoxylin. × 2 (approx.).

On section the occipital horns were considerably dilated, reaching to within 1·3 cm. of the poles. Convolutional atrophy was gross in the medial aspects of both occipital lobes, particularly about the anterior ends of the calcarine fissures (Fig.1). This was greater on the left than the right, the thickness of the cerebral substance between the meninges and the ependyma being reduced to 0·4 cm. in places. This atrophy diminished towards the poles. The normal cortical striation of Gennari was absent. Occasional small foci of atrophy were also found in the cortex of the Rolandic area on both sides, and in the frontal and temporal lobes. No further changes were observed in the cerebrum or brain-stem.

In the cerebellum there was gross atrophy of the folia in the depths of the sulci in both lateral lobes, posterior to the primary sulcus (Fig. 2), but diminishing towards the mid-sagittal plane. A mid-sagittal section through the vermis displayed a similar atrophy in the declive, and through a segment of the adjacent culmen ascending from the inter-

FIG. 3.—Mid-sagittal section of vermis. Anterior end to left. Note atrophy in declive, extending in depths of vermis to adjacent lobules. Loyez' haematoxylin. × 2 (approx.).

vening sulcus (Fig. 3). The flocculi were unaffected. The dentate nuclei appeared intact.

No changes were visible in the spinal cord.

Microscopic Examination of the Cerebrum.—The cortex of the area striata is grossly atrophied in both hemispheres. The loss of neurons here is very great in general but varies considerably in different fields. With higher magnification ($\frac{1}{6}$ in. objective) the most affected areas show fields where gliosis of varying density alone is present; in these the tissue sometimes contains small spaces (up to about 25 μ in diameter) giving a spongy appearance.

The surviving neurons are small and, although some are well-preserved, many are shrunken and distorted. No "senile plaques" or neurofibrillary changes are present.

In frozen sections stained with Sudan III there are no fat-granule cells either in the cortex or white matter. Occasional angulated microglial cells in the cortex contain a little sudanophil material; some of these lie against the perivascular sheaths of the vessels. The adjacent leptomeninges and included blood-vessels are normal both here and in all other areas examined.

The subcortical white matter is greatly reduced, but no evidence of progressive degeneration was found either in the myelin or axis-cylinders and no fat-granule cells are present. The oligodendroglial cells are in stages of acute swelling. Transition from the atrophied to the non-atrophied gyri is rather abrupt; in the latter no changes were demonstrated. But comparison between the anterior and posterior parts of the area striata shows a decline in the severity of the atrophy, and destruction of neurons, as the occipital pole is approached.

FIG. 4.—Greatly atrophied folium of lateral lobe to show destruction of granule cells, etc. Hortega's double impregnation. × 64.

FIG. 5.—Cortex at summit of atrophied part of lateral lobe for comparison with Fig. 7. Hortega's double impregnation. × 125.

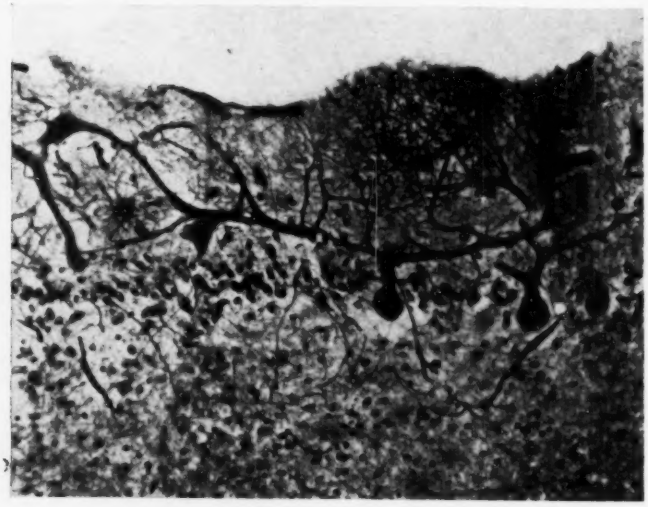
The optic radiation (left) is reduced in size but no further histological changes are present. The external geniculate body (left) appears normal. No changes were found in the optic chiasm and proximal end of the right optic nerve.

Foci of cortical atrophy, precisely similar to that seen in the visual cortex but more limited, were found in the left precentral gyrus, the right post-central and the left superior temporal gyrus. These foci affect the depths of the sulci rather than the summits and merge rather suddenly into the adjacent normal cortex.

The hypothalamus, basal ganglia, and brain-stem are not affected.

Microscopic Examination of the Cerebellum.—The cortical changes, in association with the atrophy observed macroscopically, are remarkable. In the granule-cell layer the loss of cells is profound while the Purkinje cells are in general spared (Fig. 4). The molecular layer is narrow. Proliferation of glial cells in the Purkinje-cell layer is associated with gliosis of the molecular layer. The changes are most advanced in the depths of the sulci while the cortex at the surface of the cerebellum is normal apart from a slight loss of granule cells (Fig. 5).

FIG. 6.—Atrophied cortex to show bushy area of Purkinje dendrites. Hortega's double impregnation. × 160.



The morphology of the Purkinje cells is peculiar in many particulars. In some the cell-body lies at an abnormally high level in the molecular layer, or even close to the pia, and in these the main dendrites are oblique, horizontal, or directed towards the depths of the cortex. But the dendrites of those cells that are normally situated are also abnormally sinuous, in places excessively bushy (Fig. 6) and travel for considerable distances in a more or less horizontal direction, becoming intermingled with those of neighbouring cells (Fig. 7). Often they are coarse, tending particularly to be expanded at points of branching. A notable feature is the frequent development of terminal expansions with innumerable radiating spiky processes resembling a " witch's broom " (Figs. 8, 9). These were called " stellate bodies " by Cajal (1926). They are formed on dendrites at all levels in the molecular layer, occasionally amongst the cells of the Purkinje-cell layer, and even in the borders of the granular layer. Though they are only to be seen clearly in silver impregnations they correspond, in paraffin sections stained with aniline dyes, to eosinophil masses with indefinite borders which sometimes have a vacuolated or foamy centre and are pale, like cytoplasm, with other stains such as phosphotungstic acid, haematoxylin, and Nissl. The vacuoles appear empty in frozen sections stained with Sudan III. With silver (the double-impregnation of Hortega proved most satisfactory) they contain abundant interlacing fibrils, indistinguishable from neurofibrils, which continue into the radiating processes. Approaching the more normal cortex these stellate bodies become fewer and their processes scantier.

Though the bodies of the Purkinje cells appear normal, including their content of Nissl bodies and neurofibrils, they are totally devoid of basket fibres in the most atrophied areas, and in this respect also there is a gradation to the normal cortex where these fibres are clearly demonstrated though perhaps fewer than normal. Where baskets are absent the cell-body sometimes bears a number of short, fine, lateral dendrites. Likewise climbing fibres are deficient in the atrophied cortex, with transitions to the more normal areas, and there is a concomitant loss of tangential nerve-fibres in the molecular layer.

Retraction-bulbs (" torpedoes ") are numerous on the axons of Purkinje cells ; the axon distal to this frequently bifurcates and the processes tend to loop back towards the molecular layer ; their further course cannot be determined.

In the granule-cell layer there is, in addition to the great loss of these cells, a similar loss of the Golgi cells. The areas of greatest total denudation are the seat of a loose-textured gliosis. Fine and coarse axis-cylinders, traversing this layer, are well preserved. The terminations of mossy fibres can rarely be discerned in the areas of greatest loss.

In frozen sections stained by Sudan III there is no sudanophil material in the cerebellar cortex nor in the subjacent white matter. The microglia of the cortex appears inactive.

The white matter of the folia is diminished in bulk in proportion to the severity of the cortical changes ; in the most affected areas there is some gliosis.

FIG. 7.—Atrophied cortex. Note loss of granule cells and numerous stellate bodies on Purkinje dendrites. Hortega's double impregnation. × 120.

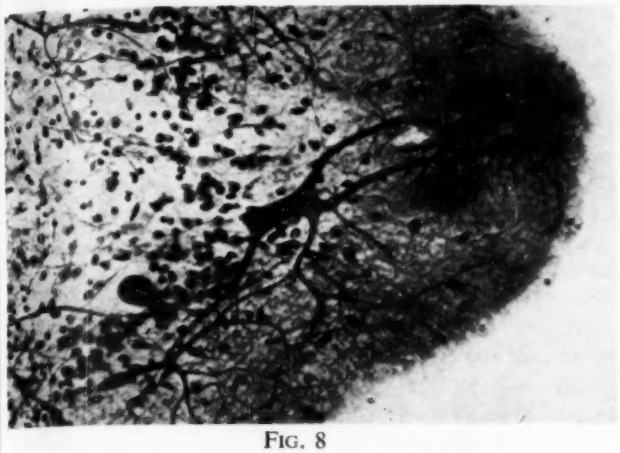


FIG. 8

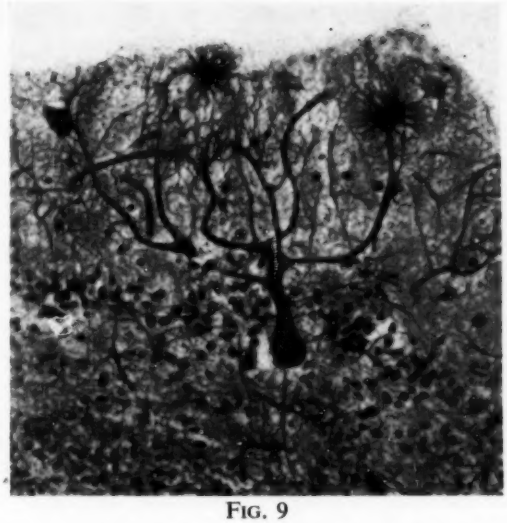


FIG. 9

FIG. 8.—Two stellate bodies on dendrites of a Purkinje cell. Hortega's double impregnation. × 180.

FIG. 9.—Purkinje cell with stellate bodies. Note absence of basket fibres around cell body. Hortega's double impregnation. × 180.

The central white matter is not appreciably reduced in bulk and appears normal microscopically. Likewise the dentate and associated roof-nuclei are not altered apart from variable degrees of chromatolysis and cell-shrinkage.

No abnormality was found in the cerebellar peduncles. The inferior olives are well preserved apart from some degree of chromatolysis and nuclear pyknosis in occasional neurons.

Microscopic Examination of Other Tissues.—The spinal cord, its nerve-roots, two posterior root ganglia (segments not identified), and the portions of sciatic and ulnar nerves are all normal.

In the kidney there is moderate focal ischaemic atrophy associated with fatty and hyaline degeneration of cortical arterioles. Fatty degeneration affects many tubules, especially the loops of Henle in the medulla.

Gross confluent back-pressure congestion is seen in the liver.

In the heart there is dense subendocardial fibrosis replacing the muscle, becoming patchy or reticulated towards the epicardium.

Diffuse back-pressure congestion is seen in the spleen.

Discussion

The clinical disturbance in the case that has been described was principally neurological; it was rapidly progressive at the onset of his illness and thereafter static. The predominant features were a gross ataxia of general distribution combined with severe concentric constriction of the visual fields. During the last years of his life the blood pressure became elevated, and death was due to heart failure, doubtless attributable to myocardial infarction.

From the pathology it is clear that the neurological disturbances are referable to destruction of neurons in the central nervous system. The constriction of the visual fields is attributable to the gross atrophy of the area striata. It is noteworthy that this is greatest about the anterior ends of the calcarine fissures, with relative sparing near the occipital poles; this would explain the preservation of central vision which is located at the posterior extremity of the visual cortex.

The ataxia must be correlated with the gross alterations in the cerebellar cortex since the posterior columns of the spinal cord, and other pathways concerned with the cerebellar apparatus, were intact. The sparing of the palaeocerebellum is remarkable, especially in the vermis, and throws some light on the problem of functional localization in the cerebellar cortex. From his analysis of gun-shot wounds of the cerebellum Holmes (1917) found difficulty in assessing the significance of lesions of the vermis because in these the lateral lobes were also involved. But he concluded that greater degrees of difficulty in phonation, articulation, and postural maintenance of the head, neck, and trunk, were associated with injuries to the vermis. If this is true, the present case suggests that the declive is a key-point of functional representation in these respects. On the other hand Holmes observed gross disturbance of speech in seven cases sustaining bilateral lesions of the cerebellum. It is generally accepted that postural sense and the coordinated movement of the limbs are represented in the ipsilateral cerebellar hemisphere. From the present case it can be argued that the neo-, rather than the palaeo-cerebellum, is here

of importance. The absence of tremor is in agreement with the observation of intact dentate nuclei (Fulton, 1938). The early sensory loss in this man's illness was perhaps due to a transitory peripheral neuropathy, suggested by the regression of numbness in the upper limbs. The demonstrable atrophy in the post-central cortex is too slight to be significant.

Since it is argued that the damage to the brain in this case is directly referable to the toxic action of organic mercury compounds it is difficult to account for the localized nature of the degeneration ; it can only be suggested that the affected areas were, for some reason, more susceptible. This suggestion, however, leaves unexplained the curious sparing of the folia at the surface of the cerebellum (Figs. 2, 3). This pattern is sometimes observed in cortical atrophy following severe anoxia, and may then be attributed to the remoter situation of the tissues in the depths of the sulci in relation to the arterial blood-supply. In the present case the degeneration and atrophy might have been expected to be the reverse of this, unless organic mercury compounds in the circulating blood enter into some chemical combination that produces an anoxic effect. We have no knowledge of such a possibility nor does it appear probable since it is rather the Purkinje cells of the cerebellum that are susceptible to anoxia.

The " stellate bodies " on the dendrites of the Purkinje cells, which are such a conspicuous feature in the present case, have been described in a subject aged 15 suffering from familial idiocy (Nageotte and Léon-Kindberg, 1910) ; in a woman of 65 with dementia praecox complicated by uraemia (Cajal, 1926) ; and in juvenile familial idiocy (Norman, 1940 ; Ule, 1952). These curious formations, and the other dendritic proliferations observed, are probably the regenerative response of the Purkinje cells to the loss of stimuli provided by climbing and basket fibres which, as described above, are lacking in these areas (see Ule for discussion and literature). The source of origin of the climbing fibres is controversial (Strong and Elwyn, 1943) ; the present case suggests that they arise from the granule-cell layer, but from which element therein cannot be determined.

The degeneration and atrophy of the granule-cell layer is thus the determining factor in the cytological changes that have taken place in the cerebellar cortex. The prime interest of the present case is that this, as far as we know, is the first occasion in which such a degeneration in man has been attributed to an exogenous toxin. In the human examples of granule-cell degeneration and atrophy the abnormality is usually manifest in infancy and may be familial. In animals there is evidence of a genetic factor (e.g. in Hereford calves, Innes, Russell, and Wilsdon, 1940). In this connexion it is pertinent to recall the animal experiments which we have already described (1940). In our series of rats focal degeneration of the granule-cell layer was observed at 11 days and, in an animal kept alive for 12 weeks, this layer contained calcospherites. This degeneration however appeared later, and seemed of subsidiary importance to a profound degeneration of the posterior spinal roots, the peripheral nerves and, later, the posterior columns of the spinal cord. We therefore surmised, though erroneously, that the pattern of the degeneration in man proceeded along similar lines. But in the present case there is no evidence of degeneration either in the peripheral nerves or in the posterior columns.

We have here an excellent example of the fallacy incurred in the application of experimental work upon lower vertebrates to disease in man. The rhesus monkey, on the other hand, showed an intense degeneration of cortical neurons in the cerebrum, but the cerebellum was not obviously affected. In this animal, however, the course of the intoxication was very acute and it is possible that, with a longer period of survival, cerebellar cortical changes would have become demonstrable.

Our present case has shown that, in conformity with the rhesus monkey, the cerebral cortex was involved, though very unequally and with a particular impact upon the visual cortex. In the cortex of the neocerebellum the granule-cell layer was selectively involved, producing a picture already well recognized in certain juvenile cases with mental deficiency. From the clinical details of the case, and from the analogous findings in our previous experiments upon rats, it cannot be doubted that this cerebellar degeneration was an acquired lesion and that it was attributable to intoxication by organic mercury compounds.

Of the remaining three cases observed and recorded in our report (1940) Case 2, A.H., was last seen in May, 1954 ; his condition has remained unaltered since he was discharged from hospital. In Cases 1 and 2 the neurological disability was less severe ; the subsequent course of these two patients is unknown.

Summary

The clinical history and ultimate pathological findings have been related in a man who suffered severe neurological disturbances from industrial exposure to methyl mercury compounds 15 years before death.

The generalized ataxia was referable to cerebellar cortical atrophy, selectively involving the granule-

cell layer of the neocerebellum, while the concentric constriction of the visual fields was correlated with bilateral cortical atrophy in the area striata.

While this form of cerebellar atrophy has been recognized in cases of juvenile familial idiocy, we believe the present case to be the first in which it can be attributed, as an acquired lesion, to an exogenous toxin.

We wish to express our thanks to Dr. S. P. Meadows for his clinical observations, to Dr. Keith Simpson for details of the necropsy and for preservation of material for histological examination, and to Dr. R. J. Calvert for his effective cooperation and clinical notes from Whipps Cross Hospital. The photomicrographs were made by Mr. A. John King.

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THE ABSORPTION AND EXCRETION OF RADIOCOPPER IN HEPATO-LENTICULAR DEGENERATION (WILSON'S DISEASE)

BY

W. B. MATTHEWS

From King's College Hospital, London

Hepato-lenticular degeneration stands almost alone among diseases of the nervous system in the wealth of biochemical information available, but there is, as yet, no generally acceptable explanation of the underlying disorder of metabolism. Any such theory must take into account all the biochemical abnormalities so far discovered. The disease is an inborn error of metabolism transmitted by recessive inheritance (Bearn, 1953). Copper accumulates in the liver and brain (Cumings, 1948) and cornea (Brand and Takats, 1951) and, paradoxically, the urinary excretion of copper is greatly increased (Mandelbrote, Stanier, Thompson, and Thruston, 1948). This excretion is more than offset by diminished elimination in the faeces, resulting in a strongly positive copper balance (Zimdahl, Hyman, and Cook, 1953). The normal specific copper plasma protein, caeruloplasmin, is largely deficient (Scheinberg and Gitlin, 1952). The results of treatment with dimercaprol (B.A.L.) reported by Denny-Brown and Porter (1951) leave little doubt that the neurological symptoms at least are due to copper poisoning. In addition to these abnormalities of copper metabolism the disease is characterized by renal amino-aciduria (Uzman and Denny-Brown, 1948) and by the presence of specific peptides in the urine (Uzman and Hood, 1952 ; Uzman, 1953).

Opinion is divided as to whether the accumulation of copper in the body is of primary importance or is merely secondary to some other metabolic disorder which is itself responsible for the lesions in the liver and brain. It is therefore important to establish whether this accumulation is due to over-absorption of the metal or to undue retention in the tissues. Zimdahl and others (1953) claimed to have demonstrated over-absorption but their results could equally be explained by failure of the normal route of excretion into the intestine. Their method of copper balance on a varying copper intake does not permit distinction between faecal copper that has passed through unabsorbed and that which has been excreted into the intestine. To do this it is necessary to follow the fate of a single dose, which may be attempted either by giving a loading dose to a patient already established on a constant copper intake, a difficult task, or else, as suggested by Matthews, Milne, and Bell (1952), by using radioactive copper, ^{64}Cu.

There are numerous difficulties in such an investigation. The isotope can only be obtained as a small proportion of inactive carrier and has a short half-life of 12·8 hours. Other limiting factors are the potential toxicity of copper, the possible effects of radiation, and the small number of patients with this uncommon disease available for investigation.

Clinical Material

Two patients were investigated. Both were young adult males with the more chronic " pseudo-sclerotic " form of the disease, and showed the characteristic amino-aciduria and increased urinary copper. Serum copper levels were within or below the normal range. Hepatic disease, as estimated clinically and by liver function tests, was not obvious in either case. Case 1 was almost symptom free following repeated courses of B.A.L. and continuous glycine by mouth, but Case 2 was severely incapacitated. Three adult male volunteers with unrelated chronic neurological disease and one normal subject acted as controls. It was not thought that the doses of copper employed would prove toxic to the patients as the lower dose was roughly equivalent to one day's urinary output on B.A.L. and very much larger quantities had repeatedly been removed from Case 1 by courses of treatment. In fact, no toxic effects attributable to copper were observed.

Methods

Radioactive copper, ^{64}Cu, was received from the Radiochemical Centre, Amersham, as a solution of copper sulphate. A known fraction was removed as a standard and the remainder given to the subject by mouth in about

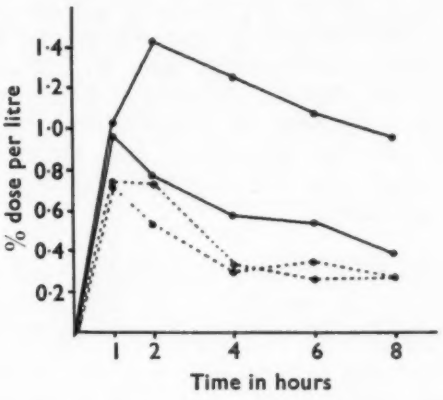
200 ml. of water three hours after a light breakfast. Two series of experiments were carried out. In a preliminary trial 1·2 mg. of labelled copper with an approximate activity of 25 μC was given to the two patients and to two controls. The general shape of the plasma curve was investigated and urine was collected as passed in the first few hours following ingestion, but the activity was not sufficient for elimination in the faeces to be followed for long enough with the apparatus available. In the second series 4·95 mg. of labelled copper with an approximate activity of 125 μC was given to the two patients and to two different controls, together with a carmine marker. Plasma levels were estimated at times suggested by the results of the first experiment and 24-hour specimens of urine and faeces were collected.

Blood was heparinized and centrifuged and the activity of the plasma was counted directly in a liquid counter (M.R.C. type M6M). Urine was also counted directly. Specimens of faeces were thoroughly mixed and approximately 5 g. portions were digested by the method of Eden and Green (1940), made to volume, and counted in the liquid counter. The short half-life of the isotope necessitated rapid preparation of the specimens. It proved possible to follow the excretion in the urine for 48 hours and in the faeces for four days. The dose of radiation was considerably less than that authorized as safe by the Medical Research Council.

Results

Plasma.—Absorption curves with a peak at one to two hours were obtained (Figs. 1 and 2). The maximum levels following 1·2 mg. of copper were 1·04 and 1·13% of the total dose per litre of plasma in the controls and 1·09 and 1·19% in the patients. In the controls following 4·95 mg. of copper a smaller percentage appeared in the plasma, maximum levels being 0·72 and 0·75% of the total dose per litre as opposed to 0·96 and 1·44% in the patients. Once the peak had been reached every point on the curves in the patients was higher than the corresponding point in the controls. Following the

FIG. 2.—Copper absorption curves: results following ingestion of 4·95 mg. of copper labelled with ^{64}Cu. Broken line, controls; solid line, patients with Wilson's disease.



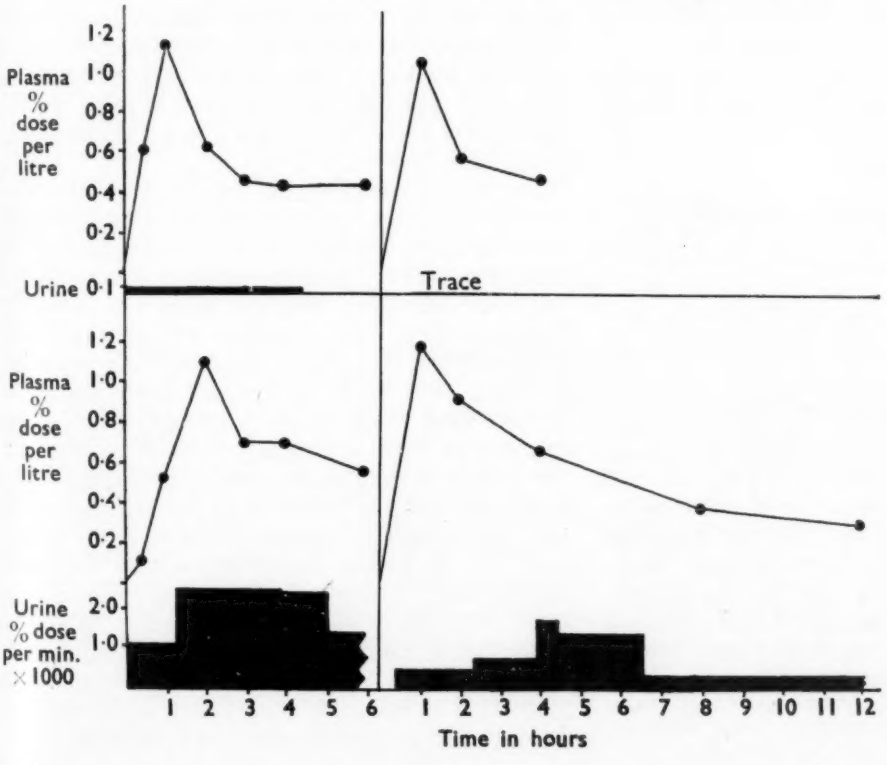


FIG. 1.—Copper absorption curves and urinary excretion: results following ingestion of 1·2 mg. of copper labelled with ^{64}Cu. Two controls above; two patients with Wilson's disease below.

larger dose considerably higher plasma levels were found in Case 2 who had developed the disease at an earlier age and in a more severe form than Case 1.

These figures do not, of course, necessarily indicate parallel changes in the total plasma copper level, and no attempt was made to estimate this concurrently. The highest level of labelled copper found in the plasma was approximately equivalent to 7 μg. of copper per 100 ml., and changes of this order could not be determined accurately by chemical means.

Faeces.—The recovery of labelled copper in the faeces after the ingestion of 4·95 mg. is shown in Fig. 3. Collection of specimens was satisfactory in

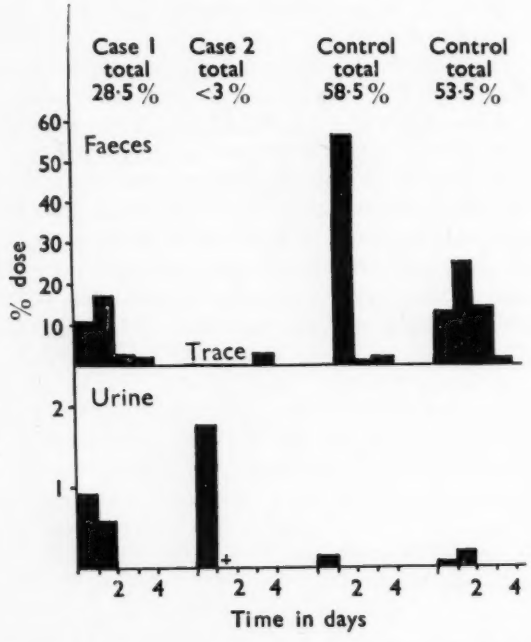


FIG. 3.—Faecal and urinary recovery of oral copper : results following ingestion of 4·95 mg. of copper labelled with ^{64}Cu.

Case 1 and in both controls but proved difficult in Case 2 in whom some degree of faecal retention could not be excluded. In view of the high plasma curve, severe disease, and high urinary excretion in this patient, and also the recovery of some radiocopper on the first day it is possible that the figure of less than 3% recovery in four days may not be misleading and the result is included. In Case 1, 28·5% of the dose was recovered and in the controls 58·5 and 53·5 %. The recovery of only small quantities on the fourth day shows that the greater part of the dose remaining unabsorbed had been recovered.

Urine.—A very striking difference in urinary excretion was found both in the 24-hour specimens (Fig. 3) and in the fractionated specimens collected during the preliminary experiment. It can be seen from Fig. 1 that this increased rate of excretion in the patients was present when plasma levels were almost identical with those of the controls at the peak of the absorption curves and continued after the peak had been passed.

Discussion

Normal Copper Metabolism.—Knowledge of copper absorption in man is scanty, partly because it is not possible to detect any rise in plasma copper by chemical means even after massive oral doses (van Ravesteyn, 1944 ; Gubler, Lahey, Cartwright, and Wintrobe, 1953). The doses of copper employed in the present investigation cannot be described as physiological in that such amounts would not normally be encountered in a single meal. They are, however, much more closely related to the normal minimum daily requirement of 2 mg. (Cartwright, 1950) than those used in previous investigations with unlabelled copper. Schubert and Riezler (1947) reported the only similar investigation in man using ^{64}Cu, but did not follow plasma levels closely in the few hours after ingestion or report individual results in detail. It is difficult to compare their results with the present figures but levels appear to have been of the same order. The results reported here suggest that a rapid initial absorption takes place and that the newly absorbed copper reaches equilibrium with pre-existing plasma copper after about four hours.

The very small quantities recovered in the urine confirm that this method of excretion is of little importance in normal copper metabolism (van Ravesteyn, 1944). Recovery of 58·5 and 53·5% of the dose in the faeces does not agree very well with the results of Schubert, Maurer, and Riezler (1948) who recovered 91% of 3·79 mg. of labelled copper in five days. The latter figure would imply that most of the normal faecal copper is derived directly from unabsorbed ingested copper. Zimdahl and others (1953) found that when copper absorption was largely prevented by means of an ion exchange resin the faecal copper was greatly in excess of the intake over a 12-day period, presumably due to the excretion of copper from body stores. In view of this large contribution of excreted copper to the total faecal copper the present figures appear reasonable. The quantity recovered undoubtedly contained a proportion of re-excreted copper but this could not be large for van Ravesteyn (1944), Schubert and

others (1948), and Marcus and Rotblat (1950) all reported a considerable delay in the intestinal excretion of more than a small proportion of copper given parenterally. Under the conditions of this test, therefore, approximately half the ingested dose was probably absorbed.

Copper Metabolism in Wilson's Disease.—Uzman (1953) has recently advanced the theory that the initial metabolic disorder in hepato-lenticular degeneration is one of proteolytic activity leading to the accumulation in the tissues of the specific peptides that he has identified in the urine. The peptides readily combine with copper and would lead to a secondary accumulation of copper in the tissues. He has suggested that the peptides, either free or combined with copper, compete with amino-acids for reabsorption by the renal tubules, thus producing both amino-aciduria and the appearance of copper-peptide complexes in the urine. He has been able to show that most of the urinary copper in Wilson's disease is actually present as such complexes. On this theory the positive copper balance would presumably be due to undue retention of copper in the tissues and not to over-absorption.

An alternative theory is that the lack of some hypothetical regulating activity normally exerted by the copper plasma protein, caeruloplasmin, which is deficient in this disease, leads to chronic over-absorption of copper from the intestine. Hepatic and cerebral damage, abnormal peptide metabolism, and renal amino-aciduria would then all be attributable to copper poisoning. There is considerable evidence that the cerebral lesions are to a large extent reversible by treatment with B.A.L., and renal amino-aciduria has recently been shown to accompany lead poisoning (Wilson, Thomson, and Dent, 1953). On either theory excessive excretion of copper in the urine might only be a late result of chronic accumulation in the body, and the discovery of amino-aciduria without excessive urinary copper in asymptomatic sibs of known cases of the disease (Uzman and Hood, 1952) cannot be used as an argument for the secondary nature of the disorder of copper metabolism.

The present investigation was designed to establish whether over-absorption of copper occurs in Wilson's disease or not. Unfortunately the small number of cases available did not allow conclusive results to be obtained. A considerably larger proportion of the ingested dose was, however, recovered from the faeces of the controls than of the patients and this finding is in favour of over-absorption, but requires confirmation in a larger series of patients.

No striking difference was found between plasma levels in the patients and in the controls, although rather higher levels were consistently found in the former. The plasma levels are the result of a number of variables including rate of absorption, rate of entry into the tissues, and rate of urinary excretion, and slight differences may therefore conceal considerable but opposing disturbances of these factors. The plasma levels therefore provide no evidence of over-absorption, but also do not suggest unduly rapid clearance of the plasma due to excessive uptake of copper by the tissues.

A very much larger proportion of the ingested dose was excreted in the urine by the patients than by the controls in spite of very similar plasma levels (Figs. 1 and 3). The problem of urinary excretion of copper was fully reviewed by Matthews and others (1952) who suggested that the plasma contains copper bound in an abnormal form able to pass the glomeruli, and the present investigation provides strong supporting evidence for this theory. Although greatly in excess of normal the actual quantities of copper recovered in the urine were very small. Case 1, after ingesting 4·95 mg. of copper, a quantity in excess of the normal daily intake, passed only 47 μg. of labelled copper in 24 hours. This patient on a normal diet habitually excreted approximately 500 μg. in the urine daily. The abnormally combined fraction of plasma copper available for renal excretion cannot, therefore, be confined to newly absorbed copper in transport. It is clear that the greater part of the urinary copper in Wilson's disease is not directly derived from the alimentary intake.*

Conclusion

The use of ^{64}Cu, despite certain disadvantages, appears to be a valuable method of investigating normal and abnormal copper metabolism. The results of this investigation are in favour of over-absorption of copper in hepato-lenticular degeneration and therefore support the theory of a primary disorder of copper metabolism. Further evidence was produced that copper exists in an abnormal form in the plasma in this disease. Ignorance of the factors responsible for the normal regulation of

* Since this paper was submitted for publication, Bearn and Kunkel (1954, *Proc. Soc. exp. biol. Med.*, **85**, 44), using ^{64}Cu, have shown that newly absorbed copper is attached to the albumin fraction of the plasma proteins. In the normal subject it is then rapidly transferred to caeruloplasmin, but in Wilson's disease this does not occur, presumably because of the deficiency of this protein. These authors also confirm that following oral administration of ^{64}Cu a higher proportion appears in the urine in patients with Wilson's disease than in normal subjects. Following intravenous injection excretion in the faeces was lower than normal. Their results are not reported in detail and the recovery of ^{64}Cu from the faeces after oral administration was apparently not attempted.

copper absorption forms one of the obstacles to a fuller understanding of the pathogenesis of Wilson's disease, and experiments with radiocopper designed to elucidate this problem would probably yield valuable results.

Summary

Copper sulphate labelled with ^{64}Cu was given by mouth to two patients with Wilson's disease and to normal controls.

A larger proportion of the ingested dose was recovered in the faeces of the controls than in the patients.

The patients passed a much larger proportion of the dose in the urine than did the controls.

Plasma levels were not strikingly different in the patients and controls but slightly higher values were found in the former.

It is concluded that there was evidence of over-absorption of copper by the patients and that copper existed in an abnormal form in the plasma.

I wish to thank Dr. S. Nevin for permission to investigate patients under his care and Dr. W. Ritchie Russell for referring Case 2. I also wish to thank Professor C. H. Gray for encouragement and the Research Committee of King's College Hospital for a grant for expenses. The work could not have been done without the scrupulous collection of specimens by the nursing staff of Fisk ward.

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ADRENALINE AND NORADRENALINE IN CEREBROSPINAL FLUID

BY

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The occurrence of adrenaline and noradrenaline in human cerebrospinal fluid (C.S.F.) has not yet been demonstrated. In this note figures for the concentration of these amines in C.S.F. are presented. Since the analysis required a substantial volume of C.S.F., i.e., 15 to 20 ml., the estimations were carried out on specimens withdrawn during air encephalography and came from patients with a suspected organic brain lesion. A small group of male schizophrenics was similarly investigated. The concentration of adrenaline and noradrenaline in plasma was determined for comparison in samples withdrawn simultaneously.

Methods

A sample of 15 to 20 ml. C.S.F. was mixed with 5 ml. of a solution containing 2% sodium fluoride and 3% sodium thiosulphate. The volume was made up to 30 ml. with 0·2 M acetate buffer *p*H 8·4, and the mixture adjusted if necessary to *p*H 8·4 by the addition of a few drops of 0·5 N sodium carbonate solution. Chromatographic purification and condensation with ethylenediamine were carried out according to Weil-Malherbe and Bone (1952), and differential fluorimetry according to Weil-Malherbe and Bone (1953). The collection of blood and the treatment and analysis of plasma have been described in the same papers.

Premedication was only given to a few of the patients in both groups. It consisted of bromide and chloral hydrate, gr. 15 to 20 of each by mouth, one hour before the investigation.

Results

The results obtained with the non-schizophrenic and schizophrenic groups of patients are shown in Tables I and II respectively. The mean concentrations of adrenaline and noradrenaline in C.S.F. are not significantly different for the two groups. Adrenaline was found in a concentration of 0·9μg./l. and noradrenaline in a concentration of 2·5 to 3μg./l. These concentrations are lower than those found in venous plasma. The concentration of plasma adrenaline is significantly lower in the schizophrenic

TABLE I

THE CONCENTRATION OF ADRENALINE AND NORADRENALINE IN C.S.F. AND PLASMA IN PATIENTS WITH SUSPECTED BRAIN LESIONS

No.	Sex	Diagnosis	C.S.F.		Plasma		$\frac{\text{CSF}}{\text{Plasma}} \times 100$	
			Adrenaline (μg./l.)	Noradrenaline (μg./l.)	Adrenaline (μg./l.)	Noradrenaline (μg./l.)	Adrenaline	Noradrenaline
1	F	Localized cortical atrophy	0·86	3·54	1·93	8·34	44·6	42·5
2	M	Epilepsy with temporal focus	0·65	1·44	2·16	8·55	30·1	16·9
3	M	Post-traumatic epilepsy with temporal focus	0·63	0·92	2·35	5·70	26·8	16·1
4	F	Psychopath	0·25	2·86	1·45	9·50	17·2	30·1
5	M	Epilepsy, mental deficiency	1·21	3·04	3·22	9·40	37·6	32·4
6	M	Epilepsy with temporal focus	0·87	2·32	2·28	6·89	38·2	33·7
7	F	Presenile dementia	1·15	2·87	2·80	5·30	41·1	54·1
8	M	Post-traumatic epilepsy with temporal focus	1·32	3·03	2·32	5·61	57·0	54·0
9	M	Post-traumatic epilepsy with temporal focus	1·13	2·16	2·40	5·55	47·2	39·0
		Mean	**0·90**	**2·46**	**2·32**	**7·20**	**37·75**	**35·42**
		Standard error of mean .	**0·115**	**0·281**	**0·166**	**0·583**	**3·942**	**4·585**

TABLE II

THE CONCENTRATION OF ADRENALINE AND NORADRENALINE IN C.S.F. AND PLASMA IN MALE SCHIZOPHRENICS

No.	Leucotomy	C.S.F.		Plasma		$\frac{\text{C.S.F.}}{\text{Plasma}} \times 100$	
		Adrenaline (μg./l.)	Noradrenaline (μg./l.)	Adrenaline (μg./l.)	Noradrenaline (μg./l.)	Adrenaline	Noradrenaline
1	–	0·51	3·47	1·15	7·52	44·4	46·2
2	–	0·93	2·87	1·84	7·30	50·5	39·3
3	–	1·57	3·72	2·53	7·90	62·5	47·2
4	–	0·96	3·10	1·44	4·45	66·7	69·6
5	–	0·91	2·17	1·73	4·87	52·6	44·6
6	+	0·45	3·64	0·81	6·82	55·5	53·4
7	+	0·85	2·62	1·41	3·85	60·4	68·0
8	+	1·28	3·45	1·97	5·90	65·0	58·5
Mean		0·93	3·13	1·61	6·07	57·2	53·35
Standard error of mean		0·130	0·193	0·187	0·544	2·746	3·937
Significance of difference group I–group II (P-value)		0·85	0·07	0·012	0·18	<0·01	0·01

group than in the non-schizophrenic group, but it would be unwise, in view of the small number of cases, to generalize about this finding. The plasma noradrenaline concentration, too, is lower in the schizophrenic group, but the difference between the two groups is not significant.

The last two columns of Tables I and II show the concentrations of the two amines in the C.S.F. expressed as a percentage of their plasma concentrations. The means of the figures for adrenaline and noradrenaline are in fairly good agreement for each of the two groups, but there is a significant difference between the corresponding means of the two groups, not only in the case of adrenaline but also in the case of noradrenaline. The schizophrenic group has a significantly higher amine concentration in C.S.F. relative to the plasma concentration.

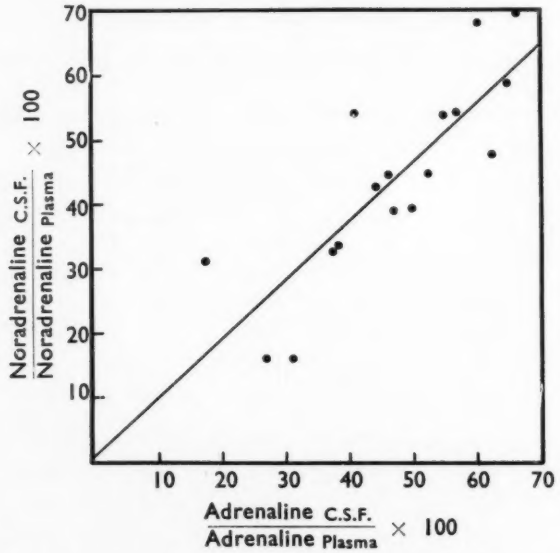

FIG. 1.—Regression of the ratio noradrenaline $_{\text{C.S.F.}}$/noradrenaline $_{\text{plasma}}$ on the ratio adrenaline $_{\text{C.S.F.}}$/adrenaline $_{\text{plasma}}$. The diagonal line is the calculated linear regression.

The percentage figures for adrenaline and noradrenaline are not always in good agreement in individual cases. In Fig. 1 the ratio adrenaline $_{\text{C.S.F.}}$/adrenaline $_{\text{plasma}} \times 100$ has been plotted against the corresponding ratio for noradrenaline, the results of both groups having been pooled for this purpose. The linear regression equation for this array is $y = 0{\cdot}95 + 0{\cdot}915\,x$, and the standard error of the regression coefficient is 0·154 ($t_{n=13} = 5{\cdot}94$). There is thus a significant correlation between these ratios. Moreover, since the regression line goes through the origin and since its slope is not significantly different from 1, there is statistical equality between the two ratios and the individual discrepancies have to be attributed to experimental error.

It also follows from adrenaline $_{\text{C.S.F.}}$/adrenaline $_{\text{plasma}}$ = noradrenaline $_{\text{C.S.F.}}$/noradrenaline $_{\text{plasma}}$ that adrenaline $_{\text{C.S.F.}}$/noradrenaline $_{\text{C.S.F.}}$ = adrenaline $_{\text{plasma}}$/noradrenaline $_{\text{plasma}}$, i.e., the ratio of adrenaline to noradrenaline is the same in C.S.F. as in plasma.

Discussion

Neither of the two groups from which the present data have been gathered can, in the nature of things,

be regarded as strictly normal. The first group consists largely of epileptics, but it also includes a psychopath and a case of presenile dementia. The schizophrenic group comprises acute and chronic cases with predominantly paranoid, hebephrenic, or catatonic features. Three of these patients have had a prefrontal leucotomy. On the other hand, none of the specimens of C.S.F. on which the estimations were carried out was abnormal with regard to total number of cells, differential cell count, protein concentration, Pandy's and Nonne-Apelt's tests for globulin, colloidal gold reaction, the Kahn test, and chloride and glucose concentrations. Since, in spite of considerable individual variation, the mean values for adrenaline are practically identical and those for noradrenaline are not significantly different in the two groups, they may provisionally be accepted as indicative of normal levels. These levels are considerably lower than in venous plasma, showing once again that C.S.F. must not be regarded as a mere ultrafiltrate of plasma, but as the product of an epithelium with specific secretory functions. The discrepancy between plasma and C.S.F. levels is, however, less marked than in the case of cortisone and hydrocortisone which occurs in C.S.F. in concentrations equivalent to 3 to 5% of their plasma concentrations (Baron and Abelson, 1954). The relatively higher concentration of adrenaline and noradrenaline in C.S.F. may be connected with their functions at the synapses of sympathetic tracts and with the fact that noradrenaline, at least, occurs in high concentration in certain parts of the central nervous system (Vogt, 1954).

The significance of the higher C.S.F./plasma distribution ratio in the schizophrenic group is difficult to assess. It is accounted for largely by a lower blood level rather than by a higher concentration in C.S.F. The permeability of the blood-brain barrier, as measured by the bromide test, tends to be decreased in schizophrenia (Walter, 1929); if the C.S.F. levels of adrenaline and noradrenaline were dependent on the same mechanism as the bromide level a lowering of the distribution ratio might have been expected.

Summary

The concentrations of adrenaline and noradrenaline in cerebrospinal fluid and plasma were determined concurrently in a group of nine patients with suspected organic brain lesions and in a group of eight chronic schizophrenics.

The mean C.S.F. concentrations in the two groups were found to be 0·90 and 0·93 μg./l. respectively for adrenaline and 2·46 and 3·13 μg./l. respectively for noradrenaline. The differences between the groups are not significant.

The plasma adrenaline concentration was significantly lower in the schizophrenic group. Conversely, the C.S.F.-plasma distribution ratio was significantly higher in the schizophrenic group for both adrenaline and noradrenaline.

The C.S.F.-plasma distribution ratio is statistically equal for adrenaline and noradrenaline. The ratio of adrenaline/noradrenaline is therefore the same in plasma and in C.S.F., adrenaline accounting for approximately 25% of the sum of the amines.

The authors are indebted to Dr. R. Ström-Olsen for his interest and encouragement, to Mr. A. D. Bone and Mrs. N. Stephens for technical assistance and to Mr. T. C. Hall for the routine investigation of C.S.F. The work has been aided by a grant for technical assistance from the Medical Research Council.

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THE TREATMENT OF MANIC PSYCHOSES BY THE ADMINISTRATION OF LITHIUM SALTS

BY

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The treatment of manic psychoses with lithium salts was introduced by Cade in 1949, following an accidental observation of a sedative-like action of lithium ions when administered to guinea-pigs. Beneficial effects of this treatment in cases of mania have also been reported by Ashburner (1950) and by Noack and Trautner (1951).

According to these reports the effects of lithium treatment are striking, and it is rather astonishing that this observation has failed to arouse greater general interest among psychiatrists. One possible reason may be that the doses reported necessary for a clinical effect are close to those giving rise to toxic symptoms. Another explanation may possibly be found in the difficulties encountered in attempts to convey to others in a quantitative manner the clinical impressions of the effect of a new psychiatric therapy. The proper evaluation of a psychiatric therapy is a matter of considerable difficulty for the following reasons: (1) An objective, quantitative assessment of the degree of the psychosis is often difficult or impossible, and usually the evaluation of the effect of a new therapy has to be based on a clinical estimate. (2) Unless special precautions are taken, the therapeutic effect and its evaluation are liable to gross distortions due to suggestibility, negative or positive, in the patients as well as in the observers. (3) Most psychoses, and notably manias and depressions, show spontaneous variations in duration and intensity. For this reason it is not always evident whether an improvement occurring concomitantly with the administration of a certain therapy is spontaneous or due to the therapy given.

The purpose of the present study has been to try out the lithium treatment of manic psychoses in such a way that these sources of error and uncertainty were reduced as much as possible.

Material and Procedure

Patients.—The material consists of 38 manic patients, 21 females and 17 males. They may be clinically divided into two groups.

Typical Cases.—These were the " pure " manias without any atypical symptoms, cases in which there was no doubt as to the diagnosis of manic-depressive psychosis at any stage of the disease. Delusions, if present, were in obvious accordance with (and most probably secondary to) the patient's mood. Hallucinations were absent or inconspicuous. Contact was always easily obtained with these patients.

Atypical Cases.—The clinical picture was more or less tainted with atypical symptoms: delusions without overt relation to the mood and probably with a katathymic background, hallucinations of more than episodic character, periods with reticence and contact difficulties, gross hysterical symptoms, etc. In all these cases, however, the course of the disease and the frequent appearance of " pure " phases did not leave any doubt as to the diagnosis of a manic-depressive insanity.

Clinical Assessment.—The patients under lithium treatment were all placed in a few special wards to ensure constancy in the observation by the ward personnel and the psychiatrists. The emotional level and the motor activity of the patients were registered daily on a three-point scale, using the values +, ++, and +++ to indicate the various degrees of the mania.

Administration of Lithium.—In some cases the lithium was given in an " open " treatment for a certain period. In other cases a " blind " scheme was adopted: the patients received lithium salts or placebos for a short period, usually two weeks; the tablets were distributed by the biochemist in boxes labelled with consecutive numbers, and neither the patients, the ward personnel, nor the psychiatrists knew whether the tablets contained lithium or were placebos. The biochemist did not see the patients or take part in the clinical evaluation. Every two weeks the medication was shifted in a random manner from lithium to placebo and vice

versa, and changes from lithium to lithium and from placebo to placebo were also used. The content of each series of tablets was not disclosed until the clinical data had been evaluated and tabulated. All tablets were of the same dimensions and colour; they were given pulverized and in a liberal quantity of sugar to cover possible differences in taste. Care was taken to ensure that all was swallowed.

The lithium salts were lithium carbonate, lithium citrate, and lithium chloride, and the tablets contained equivalent amounts of lithium; the lithium content of the tablets was checked occasionally by analysis. (Lithium chloride is highly hygroscopic and impractical to dispense as tablets. In the few instances where it was employed the tablets had to be kept in a desiccator.) The placebo tablets contained lactose, sodium bicarbonate, or potassium bicarbonate; the latter two contained carbonate in amounts equivalent to the lithium carbonate tablets.

The patients had the ordinary hospital diet without any restrictions in sodium chloride intake. Extra medication, including the use of sedatives, was avoided as far as possible, and E.C.T. was not given during the period of lithium treatment. The lithium treatment was usually preceded by a short period without any medication during which the pre-treatment clinical state was assessed.

The dosage of lithium will be apparent from the case reports. It was of the same order of magnitude as that used by Noack and Trautner (1951), although on the whole somewhat smaller, usually 24 to 48 mEq. per day, corresponding to a daily intake of 0·9 to 1·8 g. of lithium carbonate. Only in a few instances was a higher dose used.

Laboratory Tests.—In the first part of the study pulse, blood pressure, and temperature were measured daily, but later this was not found necessary as a routine. During treatment with both lithium salts and placebos the following laboratory estimations were carried out regularly, usually once a week or once every second week, but frequently more often: haemoglobin, sedimentation rate, total leucocyte count and differential count, blood urea, urine glucose, urine protein, and electrocardiogram. Serum sodium, potassium, and lithium concentrations were determined in a Beckman flame photometer (model 9200) by a modification of the method described by Beckman Instruments, Inc. (Beckman Application Data DU-12-B). The same tests were made before lithium treatment was started. In some cases the E.E.G. was recorded during lithium and placebo periods, and in a few instances the lithium concentration in the cerebrospinal fluid was measured. Both serum and spinal fluid lithium concentrations were kept secret from the observers.

Results

Psychiatric Effects.—The data from some representative cases are presented in graphs. The wavy line indicating the degree of the psychosis has been plotted according to a joint evaluation of the daily notes on emotional level and motor activity. In most cases these two varied together rather closely. In a single patient (Case 34) an unmistakable dissociation was observed during lithium treatment; the emotional level is here depicted as a line of crosses and the motor activity as a line of dots. In some of the cases part of the curve is only fragmentary because the clinical notes were too scarce to permit a proper evaluation of the degree of mania during these periods. Sometimes the clinical assessment was only secondhand, e.g., the evaluation of the patient's state before admission or after discharge, which was based on information obtained from relatives or from the patient himself; in these cases the curve appears as a broken line. The periods with "open" and "blind" treatment are not distinguished in the graphs, but usually treatment-periods of less than one month have been part of the "blind" experiment. In the legends are presented short case histories; the ages and weights refer to the time of discharge or, for the patients still in the hospital, to May 1, 1954.

The total response of each patient to the therapy has been classified as "+ effect", "possible effect", or "− effect" (Table I). In order to be classified

TABLE I
THE EFFECT OF LITHIUM TREATMENT

	No. of Cases			
	+ Effect	Possible Effect	− Effect	Total
Typical cases ..	12	15	3	30
Atypical cases ..	2	3	3	8
Total	14	18	6	38

under "+ effect" a case must fulfil one or more of the following criteria: (*a*) In a patient with manic attacks occurring at regular intervals lithium treatment was able to prevent these attacks (see Cases 1 and 2); (*b*) in a patient with constantly elevated emotional and/or motor level the degree of the mania decreased during periods of lithium administration and increased during placebo periods (see Cases 4, 5, and 6); (*c*) in a patient with a mania that changed rapidly and fortuitously in intensity

before treatment continuous lithium treatment was accompanied by a neutral period that was significantly longer than the spontaneous neutral phases (see Case 12); (*d*) in a patient with previous manic attacks of very regular duration lithium treatment brought about a significant shortening of the phase (see Case 14).

The group "possible effect" includes cases in which lithium treatment was accompanied by a distinct improvement of the condition, but in which a spontaneous cessation of the manic period could not be excluded (see Cases 15, 16, and 17), and cases in which lithium treatment appeared to influence the disease beneficially, but in which the improvement was not as clear-cut as in the cases classified under "+ effect" (see Case 28).

"Minus effect" means that treatment with proper doses of lithium (24 to 48 mEq. per day) for a proper length of time (two weeks or more) failed to influence the mania beneficially (see Cases 33, 34, and 35).

In a small number of treated patients the effect of lithium could not be established because the period of administration was too short, the dosage too small, or the observation for various reasons not quite reliable.

Our results are in essential agreement with those of the Australian psychiatrists; lithium has an unquestionably beneficial effect on a number of manic patients. So far as our observations go, they indicate that the effect is only symptomatic; when lithium administration is stopped the manic symptoms reappear unless the manic phase has subsided spontaneously in the meantime. Only in a single patient (Case 14) did we observe an effect that gave the impression of a shortening of the manic phase. A similar "curative" effect of lithium is possible in other cases (e.g., Case 15), but a proper evaluation of the effect is not possible because the spontaneous duration of the manic period is not known.

Some of the cases classified under "possible effect" have probably also reacted favourably to lithium, but the reaction could not be established unequivocally. This was the case when E.C.T. had been given so frequently or when the case history was so short that the spontaneous, i.e., untreated, course of the disease could not be estimated. Fourteen of the 18 cases in this group belong to this category. In the remaining four cases the lithium treatment appeared to influence the disease by preventing, partially or totally, manic attacks which occurred frequently and irregularly before the treatment, but the treatment has as yet not been given for a sufficiently long time to permit a classification under "+ effect".

Six patients did not respond to lithium treatment. In Case 33 the mania continued unchanged during lithium treatment whereas E.C.T. caused an improvement that was marked, if only of short duration. It cannot be excluded, of course, that treatment with higher doses of lithium and for a longer time might have been effective. Case 34 presents some interesting features; during the lithium treatment in 1952 the condition was not improved but a certain effect of lithium was probable because the patient during treatment showed a distinct dissociation between the emotional level and the motor activity. In 1954 lithium treatment was instituted once more, as short periods of lithium administration alternating with placebo periods. The patient's response was not in phase with the lithium periods, but nevertheless the condition improved gradually, and in May, 1954, the patient was in a far better condition than he had been for the last two years. It is of interest to note that even during the highest lithium dosage the serum lithium concentration in this patient never exceeded 0·8 mEq. per litre. During the first lithium period of Case 35 the mania disappeared in about three weeks, but during the second and third lithium periods (April-May, 1954) a manic attack occurred in spite of a dosage of 48 mEq. of lithium per day. This observation necessitates a classification under "− effect". Cases 36, 37, and 38 were all atypical manic-depressive psychoses and showed only insignificant clinical change during lithium treatment. In Case 36 a maximal value of 3·0 mEq. lithium per litre serum was reached; this is, with the exception of Case 39, the highest serum lithium concentration observed, and the patient had no symptoms of intoxication at the time.

The "+ effect" group includes patients with short case histories as well as very long ones, e.g., 35 years in Case 1. It will be observed, however, that with the criteria for "+ effect" employed here most of the cases with a short duration of the disease will necessarily be classified under "possible effect", even if lithium has actually been effective. It is striking that 11 of the 14 cases in the "+ effect" group were women. It may be of significance in this connexion that generally higher serum lithium concentrations were reached in the women than in the men (see laboratory findings). But our material is admittedly too small to permit any conclusions regarding the relative effectiveness of lithium treatment in cases of long and short duration, in women and men, in old and young persons.

Noack and Trautner (1951) found lithium carbonate and lithium citrate equally effective whereas lithium chloride was of much less therapeutic value.

We have mainly used the first two salts and have found that in some patients lithium citrate is apparently somewhat less effective than the carbonate; however, the number of observations is too small to warrant any definite conclusions (Table II).

TABLE II

CLINICAL EFFECT OF LITHIUM CARBONATE AND LITHIUM CITRATE

Shift of Medication		During Two Weeks after Change of Medication the Patient		
From	To	Became More Manic	Was Unchanged Manic	Became Less Manic
		Number of Observations		
Nothing or placebo	Lithium carbonate	2	11	40
Lithium carbonate	Nothing or placebo	8	9	0
Nothing or placebo	Lithium citrate	0	6	5
Lithium citrate	Nothing or placebo	6	0	0

In part of the study sodium and potassium bicarbonate tablets were used as placebos, and the dosage was such that the amount of carbonate was equivalent to the carbonate administration during treatment with lithium carbonate. Table III shows that the carbonate ion in itself is therapeutically ineffective.

TABLE III

CLINICAL EFFECT OF CARBONATE ION

Shift of Medication		During Two Weeks after Change of Medication the Patient		
From	To	Became More Manic	Was Unchanged	Became Less Manic
		Number of Observations		
Nothing or lactose	Na or K bicarbonate	0	5	1
Na or K bicarbonate	Nothing or lactose	0	9	0
Na or K bicarbonate	Na or K bicarbonate	0	4	1
Nothing or lactose	Nothing or lactose	0	4	0

The effect of lithium in cases of mania differs markedly from a simple sedation. First, in many of the cases that responded to lithium therapy rather massive doses of barbiturates and other sedatives given previously had only affected the condition slightly; secondly, when the patients had been neutralized by lithium therapy they did not give the impression of being "drugged" as patients commonly are after large doses of sedatives. Some of the patients explained, while being kept on a maintenance dose, that they "did not feel quite their own self", they were "bored" and slightly ill at ease. One patient expressed a feeling of being somehow "kept down" by the tablets. These sensations may conceivably be symptoms of an intoxication which is so slight that it does not give rise to more tangible toxic symptoms. A different explanation seems also possible. Several of these patients had been exalted and hyperactive for years before the lithium treatment was instituted. When these feelings of elation and excess of energy were gone, the patients felt changed and lacked something without being actually depressed. Only in five instances was a transition into a depressive state observed, and lithium administration was then stopped. The depression lasted from a few days (e.g. Case 16) to several months, but since these patients had previously had both manic and depressive periods, it seems doubtful whether the lithium treatment can be considered responsible for the depressions observed. Noack and Trautner (1951) found that the depressive phases of manic-depressive psychoses were unaffected or in some cases aggravated by treatment with lithium salts; for this reason we have not given lithium to depressed patients.

Intoxication.—Our observations on lithium intoxication are in agreement with the findings of Cade (1949) and Noack and Trautner (1951). The doses necessary for a therapeutic effect are not far from the doses giving rise to slight intoxication. As an example may be mentioned Case 4: when a dose of 16 to 24 mEq. lithium per day was given the mania usually abated in two to three weeks and no toxic symptoms developed. If the dose was increased to 48 mEq. per day, the patient became neutral in less than one week, but after three to four days of medication the patient experienced nausea, diarrhoea, and tremor of the hands. When the dose was again reduced to 24 mEq. per day, the toxic symptoms disappeared after one to two days while the clinical improvement lasted. Apparently 24 mEq. of lithium per day was the proper maintenance dose for this patient.

The most frequent toxic symptoms were nausea and vomiting, diarrhoea, tremor of the hands, a feeling of general fatigue, and slight drowsiness. Occasionally we observed blurred vision, vertigo, uncertain gait, slight confusion, and dryness of the mouth. Intoxication was very seldom seen on a dosage of 24 mEq. per day, whereas 48 mEq.

per day led to slight toxic symptoms in about one-fourth of the cases. The intoxication usually disappeared after a few days when lithium administration was stopped or the dose reduced. Toxic symptoms were never seen earlier than after three to four days of lithium administration.

Laboratory Findings.—The laboratory investigations in this study were made with the purpose of serving as a rough control of the treatment and a safeguard against grave intoxications. Our laboratory facilities did not permit a systematic study of the biochemical changes occurring in blood and urine during lithium treatment.

Neither the slight toxic symptoms observed in a number of patients nor the therapeutic effect of lithium treatment were accompanied by any consistent changes in the composition of blood and urine, and it may be of interest to point out specifically that lithium treatment did not induce significant changes in serum sodium and potassium concentrations. We are in complete agreement with Noack and Trautner's statement: "So far it has not been possible to find a laboratory test which would indicate optimum dosage or impending intoxication, and which could replace the careful observation of the patient."

The serum lithium level varied usually between 0·5 and 2·0 mEq./l. during treatment. A serum lithium concentration of 4·5 mEq./l. was observed in one patient (Case 39) who died from an anaemic infarction in the pons (verified by necropsy) after nine days of lithium administration. She was 71 years old, strongly arteriosclerotic, and had had one previous vascular attack during a manic explosion. Lithium treatment was instituted in the hope of preventing her frequent, violent manic outbursts. We consider it very unlikely that the lithium medication was responsible for the occurrence of the infarction but rather think that the high serum lithium level may have been caused by a sudden impairment of the patient's general biological functions.

The maximum serum lithium concentrations observed were somewhat higher in the women, excluding Case 39 (average 1·38 mEq./l., range 0·4–3·0 mEq./l., n = 21), than in men (average 1·04 mEq./l., range 0·4–1·6 mEq./l., n = 17). As mentioned before, Case 36 did not show any signs of intoxication while having 3·0 mEq. lithium/l. serum; on the other hand toxic symptoms have been observed in a patient with only 0·6 mEq./l. serum. We feel, like Noack and Trautner, that the serum lithium level is not a reliable indicator of the lithium concentration in the tissues; nevertheless, it is our impression that a knowledge of the serum lithium concentration is of some value as a guide for the therapy, and we should be hesitant to institute lithium therapy under conditions where the serum lithium level could not be checked regularly.

The lithium concentration in the cerebrospinal fluid was determined in six cases about one to two weeks after the beginning of the lithium treatment. In all cases the lithium content was lower in the spinal fluid than in the serum, the average ratio being 0·47 (range 0·33–0·67). Oberhard and Sserafimow showed in 1933 that lithium could pass the blood-cerebrospinal-fluid barrier, and Hanlon, Romaine, Gilroy, and Deitrick (1949) found in a case of lithium poisoning a spinal fluid lithium level of 1·5 mEq./l. while the serum concentration was 2·6 mEq./l.

In one patient (Case 24) lithium treatment caused transient changes in the electrocardiogram. Before treatment the E.C.G. showed slight left axis deviation but was normal in other respects. Lithium, 48 mEq. per day, was given from January 18 to January 30, 1953; on January 26 T_1 was slightly inverted and T_2 isoelectric, and on February 2, three days after lithium treatment was stopped, T_1 and T_2 were both inverted. This abnormality disappeared gradually during the following 10 days, and on February 14 the E.C.G. was identical with the one obtained before lithium administration. Lithium treatment was resumed in May, 1954, with doses of 40 mEq. per day, and similar changes occurred in the E.C.G., only less pronounced. No clinical symptoms of cardiac failure were observed during the treatment; the laboratory findings were all within the normal range, and the serum potassium level never fell below 3·5 mEq./l. Electrocardiographic changes during lithium administration in man have been described only by Hanlon and others (1949) who observed a transient intraventricular heart block in a fatal case of lithium poisoning. Radomski, Fuyat, Nelson, and Smith (1950) gave rather large doses of lithium to dogs (1·2 mEq. per kg. bodyweight). Shortly before death the E.C.G.s showed depressed S–T segments, inverted T waves, and widening of the QRS complex. It should be noted that two of our patients (Cases 6 and 32) suffered from chronic auricular fibrillation; this was not influenced in any way by the lithium administration, and the patients stood the treatment well.

Occasionally lithium treatment gave rise to slight, reversible changes in the E.E.G.; frequencies of 6 to 7 c.p.s. appeared, and the voltage was increased, but it did not exceed 100 mV. Changes of a similar type were found by Corcoran, Taylor,

and Page (1949) in a patient intoxicated with lithium.

Discussion

Lithium was introduced into medicine by Garrod (1859) for the cure of gout and of urinary calculi ; it was given in doses varying from 12 to 80 mEq. per day (Daniels, 1914 ; Hare, 1916) usually as the carbonate. The theoretical consideration behind this therapy was that, since lithium urate is easily soluble, the lithium should dissolve the uric acid deposits around the joints and in the urinary tracts. Experiments later showed, however, that lithium is only a " solvent " for urates in concentrated solutions (Good, 1903), and lithium therapy of gout and uric acid calculi has now been abandoned.

Lithium bromide has been used against epilepsy in doses of 4 to 45 mEq. per day (Squire, 1916 ; Mitchell, 1870), but the alleged superiority of lithium bromide over other bromides does not appear to have been clearly demonstrated.

Some years ago lithium chloride was widely used as a taste substitute for sodium chloride in patients with cardiac disease who had to be kept on a salt-free diet. In a clinical trial with controlled doses of lithium chloride no untoward reactions were observed (Talbott, 1950), and the substance was eventually placed at the free disposal of the patients. But in 1949 several deaths due to lithium poisoning were reported (Corcoran and others ; Hanlon and others), and the use of lithium chloride as a taste substitute has now come to an end.

Numerous toxic symptoms have been reported in the papers referred to during treatment with lithium (Cade, 1949 ; Corcoran and others, 1949 ; Good, 1903 ; Hanlon and others, 1949 ; Noack and Trautner, 1951 ; Roberts, 1950 ; Talbott, 1950) and also after experimental administration of lithium to man (Cleaveland, 1913) and animals (Foulkes, Mudge, and Gilman, 1952 ; Good, 1903 ; Masson, 1949 ; MacLeod, Swan, and Aitken, 1949 ; Radomski and others, 1950). They are listed here in an approximate order of frequency : nausea and vomiting, diarrhoea, tremor of the hands, muscular weakness and general fatigue, slight drowsiness, vertigo, uncertain gait, blurred vision, slurred speech, fasciculations in the facial muscles, mental confusion, slight depression, sweating, dryness of the mouth, tinnitus, lowering of blood pressure, reflex hyperirritability, coma, paralysis of the limbs, epileptic seizures, changes in the E.C.G. and E.E.G., lowering of body temperature, and diastolic heart stop (the last two only observed in animals).

Six deaths during lithium administration have been reported. In the first three (Corcoran and others, 1949 ; Hanlon and others, 1949), aged 70, 66, and 58, lithium chloride had been taken in excessive amounts in combination with a diet low in sodium chloride. The patients all developed coma combined with reflex hyperirritability and died less than a week later. In none of these cases was a necropsy performed. Roberts (1950) treated a chronic maniac in her fifties with 25 to 50 mEq. of lithium per day ; after a week she became confused and ataxic. Lithium administration was stopped, but the patient died on the fourteenth day after having had several epileptiform seizures. A post-mortem examination did not show any abnormalities in the central nervous system or elsewhere. Two more deaths during lithium therapy have been mentioned by Noack and Trautner (1951) but without any details. It seems likely that lithium administration has been responsible for at least some of these fatalities, but it is difficult to explain the mechanism or to identify those factors that make lithium therapy dangerous in some cases. Experiments with both man (Corcoran and others, 1949) and animals (Masson, 1949) show that restriction of sodium chloride intake should be avoided during lithium treatment, but future research will probably find additional factors that should be considered.

The psychiatric experiences with lithium are few. The authors all agree that lithium is ineffective or only slightly sedative in cases of depression and schizophrenia, but that considerable clinical improvement may be seen in cases of mania. All of the 10 cases treated by Cade (1949) responded favourably. Ashburner (1950) reports that of 50 patients treated with lithium about a dozen were able to leave hospital. Noack and Trautner treated more than 30 manic patients, and only one or two failed to show any response to the treatment. Our results are in line with these reports and show that in at least one-third of the cases the clinical improvement observed during lithium treatment is not due to inaccuracies in clinical assessment, suggestibility, or spontaneous variations.

So far the only effective treatment of mania has been electric convulsive therapy (E.C.T.), given as a series a shocks shortly after one another ; but the duration of the improvement after this treatment is often so short that the practical therapeutic value of E.C.T. is considerably smaller during manic episodes than during depressions. The lithium therapy appears to offer a useful alternative since many patients can be kept in a normal state by administration of a maintenance dose.

In an evaluation of the practical usefulness of this therapy the unquestionable toxicity of lithium has to be taken into account. The majority of the intoxications observed during lithium treatment of psychiatric patients have been only slight, and the toxic symptoms disappeared rapidly when lithium administration was discontinued. But the fact cannot be excluded that lithium therapy may be dangerous under special conditions of which our knowledge is still insufficient. A careful clinical and biochemical control of patients under lithium treatment appears advisable for the time being.

Quite distinct from the possible practical usefulness of lithium therapy in psychiatry is the theoretical significance of the observation that manic symptoms may be counteracted by the administration of lithium salts. The biochemical and physiological response of the organism to E.C.T. is complicated and largely unknown, and E.C.T. has, in spite of great expectations after its introduction into psychiatry, been of very limited value in the furtherance of our understanding of the pathophysiology of the manic-depressive psychosis. The administration of lithium salts appears to be a much less complicated procedure, and it does not seem unreasonable to expect that a study of the metabolic fate and the biological effects of lithium in experimental animals and in tissue preparations may yield useful information regarding the mechanism of its action in manic patients. Work along these lines is in progress in this hospital.

Summary

The effect of lithium salts on manic psychoses has been tested in a controlled experiment. During treatment the patients were under close clinical observation, and the effects of suggestibility were minimized by an alternation between periods of lithium and placebo administration; neither the patients nor the observers were told whether the tablets given contained lithium or were placebos. The effect of the treatment was evaluated with due consideration of the spontaneous course of the disease in each case.

Thirty-eight manic patients were treated. The response of 14 patients was classified as " + effect "; in these cases it was highly improbable that the changes occurring during the treatment were due to spontaneous variations. Eighteen patients were grouped under the heading " possible effect "; the condition was improved during lithium administration but a spontaneous cessation of the mania could not be excluded. In six patients lithium treatment did not influence the mania beneficially; these were classified as " — effect ".

The therapeutic doses of lithium varied usually between 24 and 48 mEq. per day. On the higher dosage symptoms of slight intoxication were seen in some cases, the most frequent toxic symptoms being nausea and vomiting, diarrhoea, tremor of the hands, a feeling of general fatigue, and slight drowsiness. The symptoms of intoxication disappeared in three to four days when lithium administration was stopped.

Serum lithium levels were usually between 0·5 and 2·0 mEq./l. during treatment; the lithium content of the spinal fluid was considerably lower. In some patients lithium treatment gave rise to slight, reversible changes in the E.E.G.; in a single patient transient inversions of the T waves in the electrocardiogram were observed during the treatment.

It is concluded that lithium administration may be of considerable therapeutic value in a number of manic cases, but the danger of lithium intoxication necessitates a careful clinical and biochemical control.

Finally it is pointed out that the beneficial effect of lithium in cases of mania appears to offer new possibilities for a study of the pathophysiology of the manic-depressive psychoses.

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Addendum

Since the manuscript was finished the following reports have come to our attention.

Despinois and de Romeuf (1951) and Deschamps and Denis (1952) reported good effects of lithium treatment in 10 and in four cases of mania respectively, and Lafon, Duc, and Maurel (1953) observed a sedative effect of lithium in cases of mania and schizophrenia. Carrère and Pochard (1954) found lithium of value as a sedative in eight cases of psychomotor excitation of various origin. Glesinger (1954) treated 104 patients with 7 to 43 mEq. of lithium per day. Of 21 manic patients, five responded very well, 10 responded well, and six failed to respond. Of the remaining patients, mostly schizophrenics, more than half responded very well to the treatment. About one-fourth of the patients had transient proteinuria. Gastro-intestinal symptoms were seen in seven patients and neurological symptoms (including nystagmus) in four patients, of whom one died. The necropsy showed encephalopathic changes.

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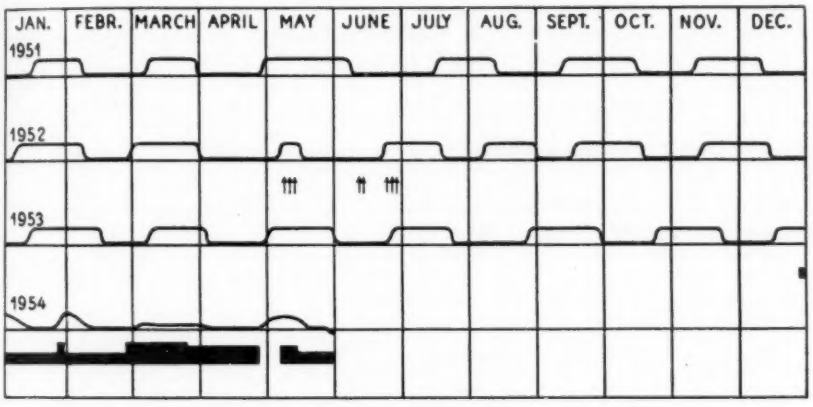
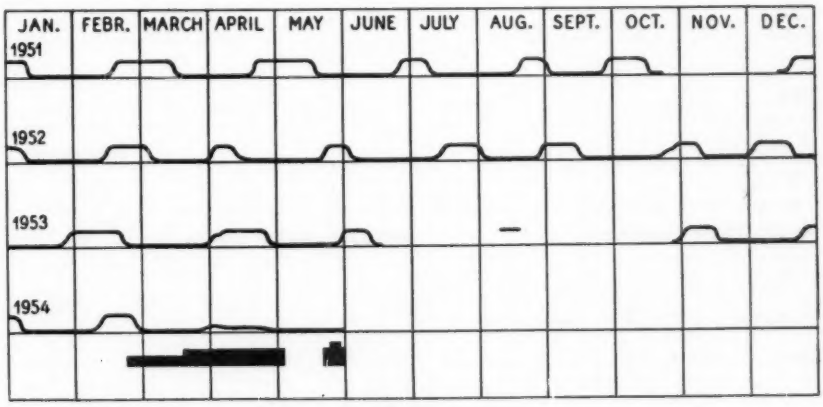
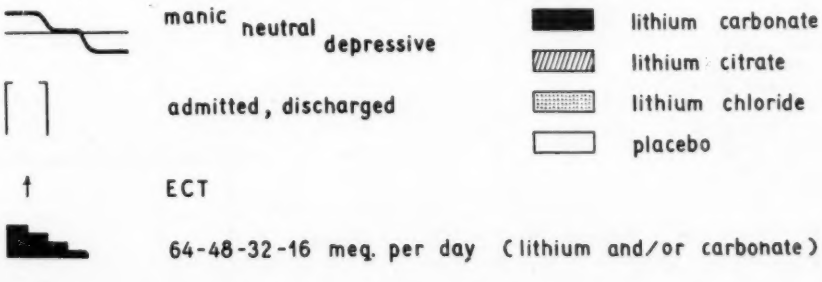
Graphic Summaries of Representative Cases

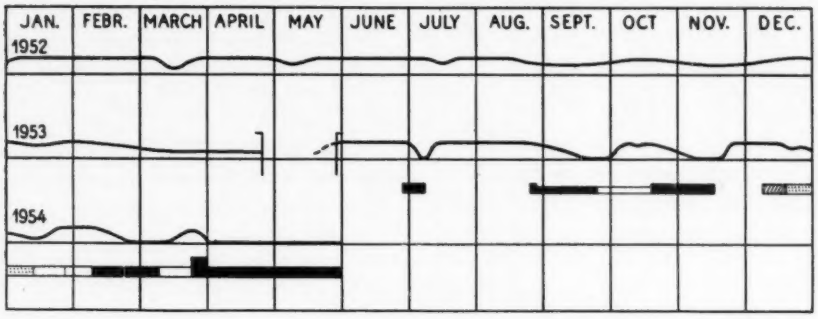


Case 1.—A woman, aged 61 (70 kg.), has been in a mental hospital for the last 35 years with regular attacks of mania. She has never had depressions.

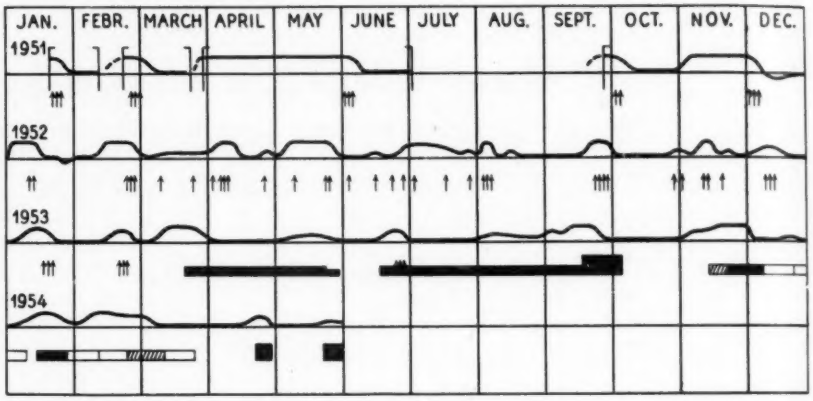
Case 2.—A man, aged 52 (67 kg.), at 23 and at 30 years of age had depressions of short duration. For the last 21 years he has been in a mental hospital with regular attacks of mania but no depressions.



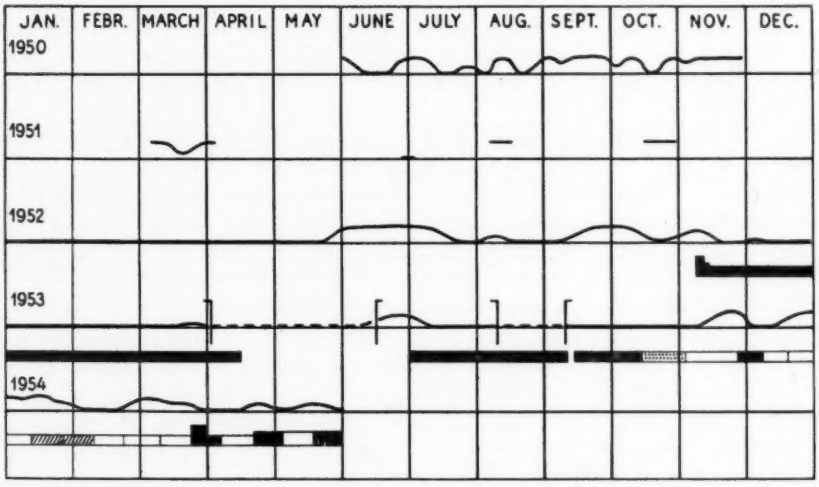




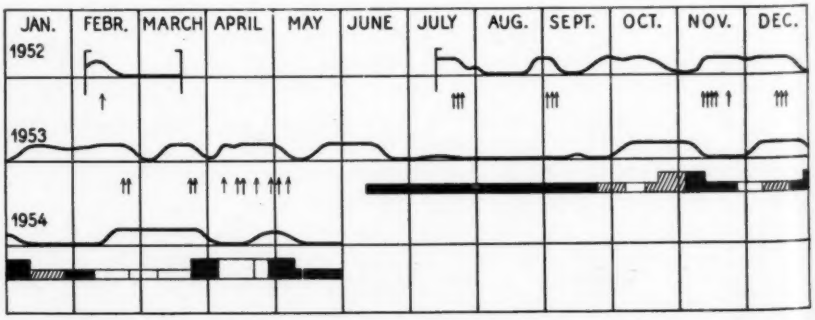
Case 4.—A woman, aged 68 (72 kg.), at the age of 22 was depressed for one month. She was in a mental hospital for two years at 52–54 with irregular phases of mania and depression. From her sixty-second year she has been in a mental hospital, and during this time she has been almost constantly manic with only very brief neutral intervals.



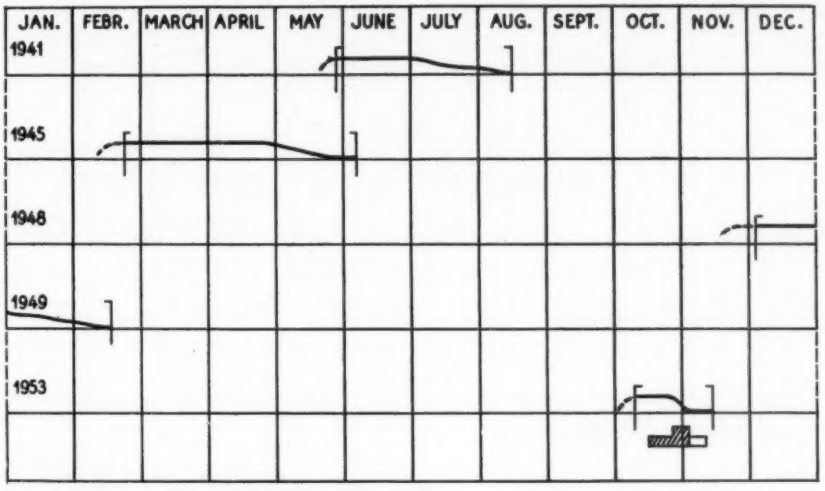
Case 5.—A woman, aged 43 (53 kg.), had her first manic attack at 30. Since then she has had frequent manic periods, varying in duration from a few months to some years, alternating with neutral phases. She has never had depressions.



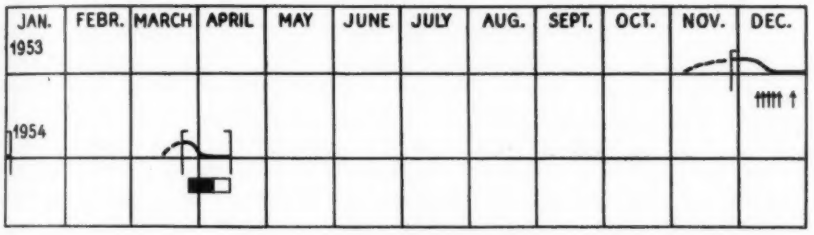
Case 6.—A woman, aged 60 (75 kg.), at 45–46 had a manic phase lasting one and a half years. For the last 10 years she has been in a mental hospital almost constantly. Her mania has been changing irregularly in intensity, and the neutral phases have been of rather short duration. She has never had depressions. Since the age of 55 she has had auricular fibrillation, which has remained well-controlled on digitalis treatment.



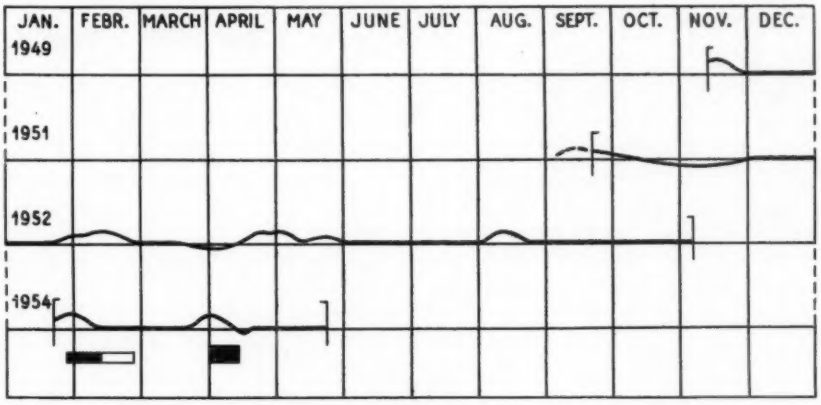
Case 12.—A woman, aged 63 (70 kg.), had short uncharacteristic psychotic episodes at 16 and at 30. She had severe manic attacks of several months' duration at ages 49, 56, and 57. In February, 1952, she had a short manic phase, and since July, 1952, she has been in a mental hospital.



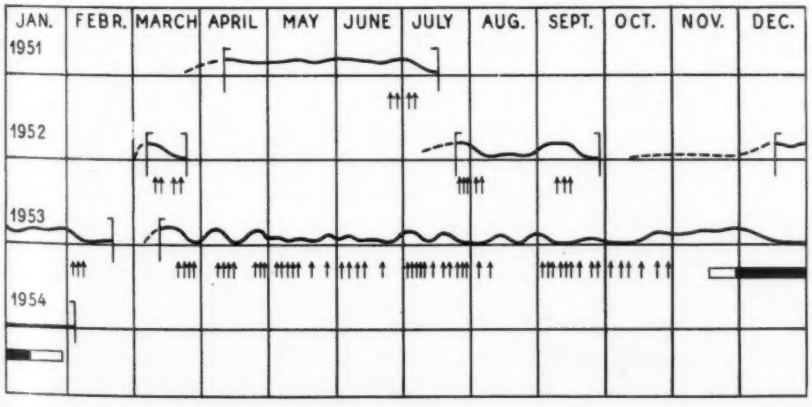
Case 14.—A woman, aged 50 (87 kg.), during a pregnancy at the age of 34 had a manic period of some months' duration. At ages 38, 42, and 45 she had manic phases which lasted three months each. She has never had depressions.



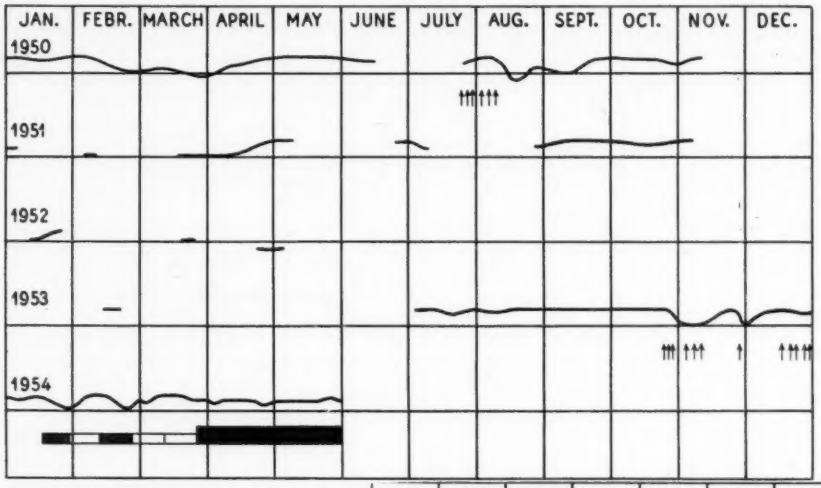
Case 15.—A woman, aged 48 (61 kg.), had no psychotic phases before admission in 1953.



Case 16.—A man, aged 62 (69 kg.), at ages 26 and 45 had manic attacks of short duration. For the last eight years he has had irregular manic phases of one to two months' duration alternating with rather long neutral phases and with depressions lasting a few days.

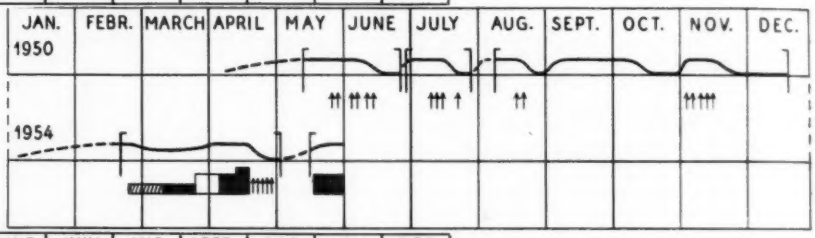


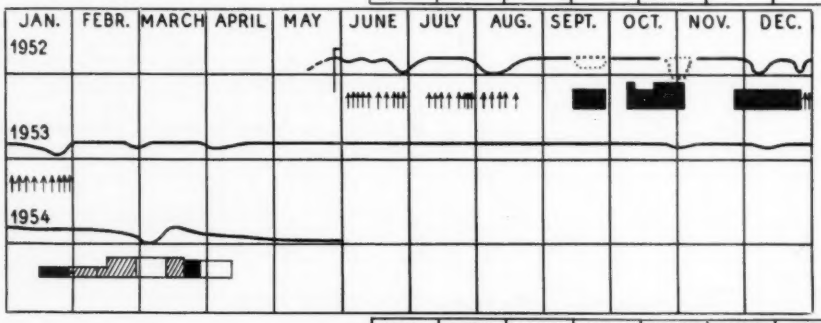
Case 17.—A woman, aged 40 (52 kg.), at the age of 35 was in a mental hospital for eight months with a depression which later changed into a mania. Since 1951 she has had several manic phases but no depressions.



Case 28.—A man, aged 26 (61 kg.), had a psychosis which started at the age of 20, and he has been in a mental hospital since then. Manic phases have alternated irregularly with short neutral or slightly depressed periods. The patient is probably feeble-minded, and the clinical picture is that of an atypical manic-depressive psychosis.

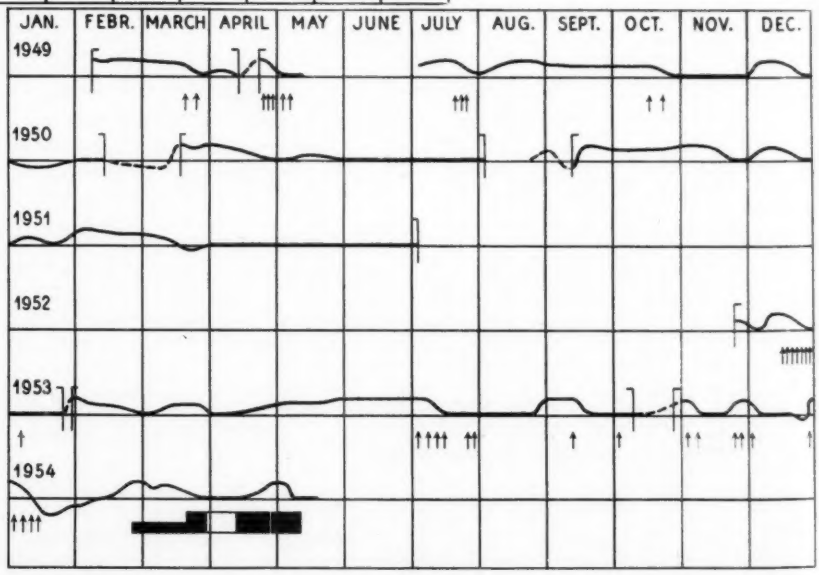
Case 33.—A woman, aged 42 (70 kg.), had depressions of two to three months at ages 15, 24, and 26. From her thirty-third to her thirty-ninth year she had frequent manic attacks of several months' duration and with only brief neutral intervals. She was healthy during the following three years, but in January, 1954, she became manic again.





Case 34.—A man, aged 45 (68 kg.), had no psychotic phases before admission in 1952.

Case 35.—A man, aged 55 (80 kg.), from the age of 21 had occasional periods of hypomania and slight depression, and at ages 40, 42, and 46 severe depressions. For the last seven years he has had frequent, irregular, severe manic attacks and a few short and slight depressions. During the last three years he has had four or five epileptiform seizures.



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THE SEQUELAE AND SHORT-TERM PROGNOSIS OF ATTEMPTED SUICIDE

THE RESULTS OF A ONE-YEAR FOLLOW-UP OF 200 CASES

BY

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Dahlgren (1945) in Sweden, and Stengel and his associates (Stengel, 1952) in London, have previously reported systematic follow-up studies of cases of attempted suicide. Dahlgren studied 230 individuals, of whom 14 committed suicide within four years (15 were untraced), Stengel 138, of whom one committed and 17 attempted suicide within five years (11 were untraced). No attempt will be made here to summarize the other detailed findings of these investigations. The importance of such studies for the clinical assessment of suicidal attempts and for the validation of methods of their management needs no emphasis.

The present investigation is the second of its kind to be reported in this country, and has been made by those who originally investigated the suicidal attempts. This latter circumstance has enabled us to trace 199 of the 200 individuals involved. The results of the first year's follow-up are now recorded, since for practical purposes the short-term prognosis is of greatest importance.

The Case Sample and Method of Follow-up

Two hundred consecutive cases of attempted suicide admitted to the observation ward of a general hospital in the years 1950–52 were personally investigated at the time of their suicidal attempts, and have been followed-up one year later. The large majority of all persons attempting to commit suicide in the city of Edinburgh are admitted to this hospital, and it is likely that the sample is as representative of an urban population as it is possible to obtain.

The sex, ages, and diagnoses of the cases are detailed in Table I.

The follow-up investigation has been conducted, except in those cases to be mentioned, either by personal re-examination of the patient, or by interviewing the nearest relative or other responsible and informed person. In six cases a psychiatric social worker in another part of the country made a home visit for us; in two cases we got a written report from the individual's general practitioner; and in two further cases a written account from another reliable informant. Only one man could not be traced. His death has not been registered. All relevant hospital documents have been scanned.

TABLE I
SEX, AGE, AND DIAGNOSIS OF CASES

Age	Male	Female	Total	Diagnosis	Male	Female	Total
15–19	4	2	6	Depressive state	41	71	112
20–29	22	26	48	Psychopathic state	25	17	42
30–39	17	21	38	Epilepsy	3	9	12
40–49	17	14	31	Schizophrenic and paranoid reaction	7	4	11
50–59	16	21	37	Organic reaction types	2	3	5
60–69	10	15	25	Mental defect	5	—	5
70 and over	6	9	15	Others*	9	4	13
Total	92	108	200	Total ..	92	108	200

*"Others" includes some individuals near psychopathic and some near normal.

Period in the Observation Ward

One hundred and six (53%) of the group were detained in the general hospital for one week or less, 69 (34·5%) were detained for one to two weeks, and 25 (12·5%) were detained for more than two weeks. Of those detained over two weeks, three-fifths were discharged home.

Six (three men, three women) died in the observation ward. Of these, three were admitted to hospital when suffering from advanced disease of the central nervous system; the other deaths were due to respiratory or cardiovascular disease. This early mortality rate of 3% compares with the 5·9%

reported from Liverpool (Hopkins, 1937) and the 5% from London (Stengel, 1952).

Disposals from the Observation Ward

One hundred and ninety-four individuals were discharged from the observation ward. Their disposals are given in Table II.

TABLE II
DISPOSALS FROM OBSERVATION WARD

Disposal	Male	Female	Total
Discharged home	51	63	114
Transferred to mental hospital as			
Voluntary patient	21	27	48 } 55
Under certificate	2	5	7 }
Transferred to neurosis clinic or nursing home..	13	9	22
Others*	2	1	3

*" Others " includes returned to Service unit, returned to prison, admitted to hospital for incurables.

These disposals may be contrasted with those of two comparable series investigated in this country (Table III).

TABLE III
DISPOSALS COMPARED WITH TWO OTHER SERIES

Investigation	Batchelor, Edinburgh (1950–52)	Hopkins, Liverpool (1932–35)	Stengel, London (1946–47)
Total no. of cases ..	200	656	138
Discharged home ..	57%	57·3%	19·6%
Transferred to mental hospital	27·5%	10·7%	72·5%
Of these, certified insane	12·7%	100%	38%
Transferred to other hospitals	11·5%	10·4%	2·9%
Discharged to police ..	nil	15·7%	nil

In addition to the 55 individuals transferred directly from the observation ward, 10 others (5%) were admitted to mental hospitals later in the first year. Of those discharged home from the observation ward, 61% were treated and investigated further as out-patients by the investigators.

Deaths by Suicide

Certainly three, probably four, individuals committed suicide in the year following their suicidal attempts; three of the four had been admitted to hospital because the risk of a further attempt had been recognized.

Case 29.—This patient was a single woman, aged 25, suffering from a psychopathic state. Her abnormality had become apparent at an early age and was characterized by pathological lying, truancy, vindictiveness, petty crime, sexual promiscuity, and numerous changes of job. Periods spent in an approved school and at a neurosis clinic failed to modify her behaviour. Early on a New Year's Day at a party she swallowed barbiturate tablets which she was carrying in her pocket. Her suicidal intent seemed minimal. Apparently she had acted in pique, feeling that she was getting insufficient attention. Discharged home, she became estranged finally from her family, and frequented hotels where she deceived people into believing that she was a titled lady. Four months later, in a hotel in another town, she committed suicide by potassium cyanide poisoning.

Case 69.—A widow, aged 60, had developed an intractable involutional melancholia after the death of her husband in 1947. She had attempted suicide by coal-gas poisoning in 1949 and was treated in a mental hospital for two months. In 1950 her only daughter became engaged to be married, and subsequently, on more than one occasion, the patient threatened to strike her daughter with an axe. In April, 1951, twice in one morning, she attempted to hang herself in her kitchen, and was twice cut down when nearly dead. Readmitted to a mental hospital under certificates, she called herself a criminal, at times blamed her daughter, and stated that she had been dominated by a fear of injuring her daughter. In November, 1951, two months after her discharge from hospital apparently recovered, she hanged herself in the waiting-room of a railway station. Her daughter broke off her engagement after her mother's death.

Case 143.—A widow, aged 57, had developed an involutional melancholia four months before, apparently precipitated by her own decision to turn out of her home a psychopathic daughter and her illegitimate child. She made a determined suicidal attempt by cut throat in a psychological setting of great guilt, fears of insanity, and identification with her dead husband. Admitted to a mental hospital, she was discharged after three months apparently well. Eight days later she committed suicide by cut throat.

Case 177.—An unemployed man, aged 64, attempted suicide by barbiturate poisoning. Suffering from a manic-depressive psychosis, his depression had been characterized by insomnia (with great concern about it), feelings of increasing physical incapacity associated with chronic bronchitis, and loneliness (though married, he was living alone). Two years before he had been a patient in a mental hospital following a suicidal attempt by poisoning. Readmitted to a mental hospital as a voluntary patient, he was discharged recovered two months later. Seven months after the second suicidal attempt he was admitted semi-comatose to a general hospital and, without regaining consciousness, died after two days. The diagnosis recorded was " probable bronchopneumonia ": the possibility of his having poisoned himself was not recognized. He had continued to live alone, since his wife had a resident occupation.

It will be noted that two of the women were suffering from depressions in late middle-life : both were widows, and in each case the breakdown was related to an ambivalent relationship with a daughter, involving marked aggression and intense feelings of guilt. Despite apparently successful psychiatric treatment, they broke down again after re-exposure to the situation which had elicited their intense affects. The suicidal attempt of the psychopathic young woman might have been dismissed as a mere gesture. It is likely that ostracism by her long-suffering family was a potent factor in precipitating her suicide. Though suicide cannot be proven, the old man died in circumstances which suggest that his death was by suicide. Loneliness and estrangement from his wife were probably the major precipitating factors in his case.

Later Deaths from Other Causes

Of the 15 individuals who died from other causes after discharge from the observation ward, four died within three months, five within three to six months, and six within six to 12 months of their suicidal attempts.

A woman, aged 25, died of the pulmonary tuberculosis from which she had suffered for some years, and a woman, aged 39, died following a partial gastrectomy for peptic ulcer. The other 13 individuals were beyond middle-age : eight were aged 60 years or over. Causes of death in these 13 were : arteriosclerosis and senility, four ; coronary thrombosis, four; pneumonia, three; and cancer, two.

Further Suicidal Attempts

Seven individuals (two men, five women) made further suicidal attempts. Their histories can be sketched briefly.

Case 4.—A man, aged 65, unemployed, separated from his wife and living alone, had been depressed for some months. Due to appear in court for arrears of rent, he attempted suicide by gassing. His previous history revealed evidence of an inadequate psychopathic state, with passive homosexual trends. Discharged home, he attended as an out-patient and improved. Seven weeks later, when the psychiatrist went on holiday, he relapsed and again attempted suicide by cutting his wrists. He was then admitted to an old people's home and has kept well.

Case 23.—A woman suffering from an aggressive psychopathic state, married at the age of 40 a widower. Unable to adapt herself to married life she was frigid, felt tied down, and disliked intensely her three step-children. Two years later, after a quarrel with her husband, she made a determined suicidal attempt by aspirin poisoning. Admitted to a mental hospital as a voluntary patient, she continued to be aggressive and suicidal, and discharged herself within a month. Nine days later, following another quarrel with her husband, she again attempted suicide by coal-gas poisoning and was readmitted to a mental hospital.

Case 33.—A single man aged 31, suffering from epilepsy with gross emotional instability, attempted suicide by barbiturate poisoning after minor thwarting. He was unemployable, and there was a history of five previous suicidal attempts, leading to admissions to a mental hospital. He was discharged home. Five months later he attempted to hang himself, and was readmitted to a mental hospital under certificates : he stated that he had felt " fed-up " because of his headaches and inability to work.

Case 48.—An emotionally unstable, sexually promiscuous, and intellectually dull woman, aged 38, who also suffered from epilepsy, impulsively attempted suicide by drowning after a tiff with a young man. She had twice previously been a patient in a mental hospital. On this occasion she was discharged home. Three weeks later she again attempted suicide, jumping from a second-floor window : she stated that she had had a " dizzy turn ". There being no vacancy in a suitable institution, she was again returned home.

Case 71.—A married woman, aged 44, suffering from epilepsy with personality disorder, attempted suicide by barbiturate poisoning two months after the death of one of her children. This child had been ill in bed with tonsillitis : while she was playing with him he died, and she said she might have smothered him in the bed-clothes. In the previous year she had made two suicidal attempts, the second leading to admission to a mental hospital. She was again admitted to a mental hospital as a voluntary patient. Eleven months later at home, when the Society for the Prevention of Cruelty to Children was investigating the possiblity of ill-treatment of her eldest son, she again attempted suicide by barbiturate poisoning. She was readmitted to a mental hospital.

Case 110.—A married woman, aged 36, epileptic and temperamentally grossly unstable, had made four previous suicidal attempts by jumping, barbiturate poisoning, and coal-gas poisoning : more than one of these attempts had been nearly fatal. When drunk she made a further suicidal attempt by coal-gas poisoning, after a quarrel during which she struck her husband. Admitted to a mental hospital under certificates, she remained there nine months. Six weeks after discharge she made a further suicidal attempt by barbiturate poisoning, and was readmitted to a mental hospital.

Case 148.—A married woman, aged 51, of hysterical personality, had first developed incapacitating nervous symptoms 10 years before. A chronic invalid reaction developed, with hypochondriasis and depressive moods. Overdoses of drugs were taken on several occasions. After her husband had been admitted to hospital seriously ill, she attempted suicide by barbiturate

poisoning. Mental hospital treatment was advised but refused. Seven months later she made a further suicidal attempt by the same method. Again neither she nor her relatives would agree to psychiatric treatment.

It will be noted that all these individuals were of chronically unstable temperament: four were epileptic, two psychopathic, and one showed a hysterical personality disorder of severe degree. Three received mental hospital treatment, one refused treatment, and another could not be accommodated. The characteristics of this suicidal group and their repeated attempts at self-injury have been discussed more fully elsewhere (Batchelor, 1954).

Assaults

Several men were reported as having attacked their wives. A feeble-minded man, four months after his suicidal attempt, was committed to a State institution for seriously assaulting another man. A manic-depressive and dipsomaniac patient, who had refused hospital treatment after his suicidal attempt, came to hospital one month later saying that he must be restrained since he intended to kill his wife: he had bought a knife for the purpose. Though our information about assaultive behaviour is not complete, it appears that a similar percentage of individuals commit serious assaults as make further suicidal attempts.

Social Reverberations of the Suicidal Attempts

To record the social reverberations of a suicidal attempt is difficult, and to do so completely, probably impossible. We present here a summary of some of the information we obtained about the social aspects of these attempts.

It should be noted that the large majority of those who received in-patient psychiatric care, did so voluntarily: that is, they accepted that admission to hospital either was necessary to ease their suffering or offered some hope of deliverance from an impasse. On the other hand, their suicidal attempts had compelled the attention of others to the seriousness of their sickness, and had thus facilitated more effective treatment. One may note that this is comparable to what may happen in cases of physical illness; when, for example, the sufferer from apparently trivial indigestion develops a gastric perforation which requires surgical operation. Or one may prefer (Stengel, 1952) to interpret the sequence as evidence that a suicidal attempt constitutes an appeal to society for effective help.

Most of the group were not admitted to hospital. Amongst these, a small number, about 5% of the total group of 200, improved their social positions as a result of their suicidal attempts. If their acts were attempts to manipulate the environment in a direction favourable to themselves, they seemed to achieve that purpose. We include those cases in which a spouse or lover was, when disaffected, persuaded to give the potential suicide another trial instead of leaving him; or was rendered more considerate; or when unwanted was got rid of; and those cases whose situation was improved by society undertaking their further care in a hostel or Eventide Home. A similar small proportion of the group worsened their positions. Contrary to their wishes their marriage was disrupted, a lover lost, or their family decided finally to reject them.

In about 15% of all the cases the suicidal attempt proved emotionally disturbing for several or many months to one or more of the near relatives. As would be expected, spouses, offspring, and mothers were most often affected. In at least three cases relatives required psychiatric treatment for severe symptoms. One woman herself attempted suicide seven months after her sister's suicidal attempt, and their acts were directly related.

We obtained information only about the grosser reactions of the relatives concerned, and we know nothing of what had been for the meantime repressed successfully, but which may later have a traumatic influence. However, we certainly found less severe disturbance than we had expected. We were impressed by how frequently the suicidal attempt had made no great commotion in the family group: the individual recovered from his illness and resumed easily a successful course in life; or the lamentable interchanges of a cat-and-dog existence were taken up again where they had been left off. In several cases a year later there was an improved situation to report—which had not been an outcome of the suicidal attempt—a happy marriage made, a better job found, or a new house.

Of those initially admitted to a mental hospital, 33% were discharged home recovered or relieved in the first three months, and a further 31% in the next three months. A further six individuals were discharged from a mental hospital between six months and one year after admission.

Table IV indicates that at the end of one year approximately four-fifths of those who were not in hospital were employed, and this gives some measure of the degree of readjustment which they had reached. The presence of a considerable psychopathic group, more or less stabilized and more or less symptom-free, rendered impossible a neat separation of these individuals into the two categories of " nervously ill " and " fit ".

The diagnoses of the 17 individuals who remained

TABLE IV
POSITION AT END OF ONE YEAR

	Male	Female	Total
Total group	92	108	200
Dead	12	9	21 (10·5%)
In mental hospital—			
Remaining since attempt or readmitted	8	9	17 } 27 (13·5%)
Admitted later	5	5	10 }
Out of hospital	66	85	151 (75·5%)
Employed	51	67	118 (59%)
Not known	1	—	1

in the mental hospitals to which they had been transferred from the observation ward were: depressive psychoses, nine; schizophrenia and paranoid states, six; general paralysis, one; psychopathic state, one.

Discussion

Before discussing the propriety of the disposals of these cases, we must emphasize that while the individual was still a patient in the observation ward his state was in every case thoroughly assessed from the psychiatric, physical, and social aspects. A decision about further management was made therefore on the basis of considerable knowledge. It might well be unjustifiable to dispose similarly of a group of attempted suicides who had been more superficially examined.

The majority were discharged home after a period of less than a fortnight in the general hospital. Less than one-third were admitted to a mental hospital, and, though many were technically certifiable, only seven were certified as of unsound mind. Was this rather free policy justified by its results? We believe that our follow-up study has demonstrated that it was.

Only one individual (Case 29) committed suicide, whose fatal action was quite unexpected by us, and in retrospect we do not feel that any undue risk was taken in this case. She, and all seven who later unsuccessfully attempted suicide, belonged to the chronically temperamentally unstable group, for whom we have at present no effective treatment or suitable provision: such people repeatedly hazard their lives and we cannot permanently safeguard them. The two, probably three, others who took their lives, did so after they had received mental hospital treatment.

Amongst the attempted suicides mental hospital care and treatment are required most often for those suffering from depressive, schizophrenic, and paranoid psychoses. It is more often required for those past middle-age than for younger individuals. It is necessary for the majority of those aged 60 or over, but it is not necessary for the majority of those of all ages. A policy of sending most attempted suicides to mental hospitals is in our view over-cautious, and, especially at a time of acute shortage of accommodation, wasteful. (That it was found necessary to send 73% of the group investigated by Stengel to mental hospitals underlines his statement that his group was atypical.)

The results of this follow-up emphasize once again the serious suicidal risk which accompanies the depressions of later middle-life and the senium, and which persists far into convalescence. Our experience further suggests that when a depressive psychosis has been precipitated by breakdown in a relationship characterized by intense possessive love, and when the aggression consequent upon this severe disappointment has resulted in an attack upon or other overt hostility towards that relative, the ensuing guilt tends to be of such proportions that only death by suicide can expiate it. We hope that later follow-up studies of our cases may enable us to identify other situations, internal conflicts, and reaction-types especially fraught with the danger of suicide.

Stengel (1952) has written: "There is a social element in the pattern of most suicidal attempts. Once we look for that element we can find it without difficulty in most cases." He stresses the "appeal character" of suicidal acts, considering them to be directed Janus-faced both towards a renewal of human relationships and towards death. This is a valuable formulation. Our data, where they do not confirm his findings and concepts, tend rather to qualify than to contradict them.

Stengel states that the suicidal attempt usually results in some modification of the individual's social situation: "For many patients the suicidal attempt initiates a new era in their relationship to their environment . . ." While this is undoubtedly true in certain instances, we found that it was not true of the majority of our cases, and was true perhaps only of a small minority. He suggests that the number of those who, having first attempted suicide, later kill themselves, will depend largely on the reaction of their human environment to the suicidal attempt. Here our findings support, though they are insufficient to prove, his hypothesis. In three (Cases 29, 69, 177) of the four cases of death by suicide, estrangement in personal relationships had contributed largely to precipitate breakdown: the suicidal attempt had not healed this alienation, but in one case at least (Case 29) had aggravated it. Furthermore, apparent symptomatic

recovery in a sheltered environment had not been accompanied by the necessary social readjustment, either of the individual or of his group. These facts remind us how necessary it is in cases of nervous and mental illness to understand and to treat the patient in his social context. By doing so thoroughly, we may prevent some suicides.

The appeal element is present most frequently and prominently in the suicidal attempts of certain temperamentally unstable individuals chronically in conflict with their society. It is doubtful if it is an element in all suicidal attempts. The melancholic, for example, his distress centred entirely on himself, may ignore human contacts and attempt suicide because he believes there is no other way of relief, or because his guilt seems to demand capital punishment. An over-emphasis upon the "appeal character" of suicidal attempts might lead to an under-emphasis of their danger. Further data must be obtained before we can depict definitively their characteristics, and Stengel utters a timely warning against undue optimism in prognosis. Obviously also one cannot reach a satisfactory understanding of a particular suicidal attempt by means of still rather tentative views of the general significance of these acts. The precise motives must be elicited in each case before appropriate treatment can be instituted.

Summary

Two hundred consecutive cases of attempted suicide admitted to a general hospital and personally investigated from psychiatric and social aspects have been followed up a year later. One hundred and ninety-nine were traced.

Fifty-seven per cent. were discharged home from the general hospital, and less than one-third required mental hospital treatment. This rather free policy in disposals seemed justified by its results.

One year later, 13·5% of the group were in mental hospitals, 76% were at home, and 59% were employed.

The over-all mortality in the first year, which involved mainly those past middle-age, was 10·5%. Three, probably four, individuals (2%) committed suicide.

Seven other individuals (3·5%) made further suicidal attempts. Several men committed assaults.

The detailed findings indicate that those who show persistently psychopathic behaviour are apt to repeat their suicidal attempts; that depressive psychoses carry their serious suicidal risk late into convalescence; and that social factors may play a considerable role in aggravating a suicidal trend to a fatal outcome.

The social reverberations of the suicidal attempts of the group, upon themselves and their families, are reported; and the "appeal character" of suicidal attempts is more briefly discussed.

We are grateful to Professor Sir David K. Henderson for his advice, and to Dr. J. K. Slater for permission to study these cases in his wards at the Edinburgh Royal Infirmary.

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THE EFFECT OF TEMPORAL LOBECTOMY UPON TWO CASES OF AN UNUSUAL FORM OF MENTAL DEFICIENCY

BY

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In 1898, when giving the final particulars and the necropsy findings of a case of epilepsy which fully exemplified dreamy states and automatisms, Hughlings Jackson (1931a) wrote that there were post-epileptic actions " of a kind which in a man fully himself would be criminal ". But another 25 years were to elapse before Penfield began his studies on brain-scars (Penfield and Erickson, 1941) which were eventually to secure for surgery a place in the treatment of epilepsy. At first the operations were restricted to those patients resistant to medical treatment in whom there was conclusive evidence of a focal scar, usually the result of a head injury. With the introduction of electrical recording devices, the field of surgery has been extended so that now the indications for operation comprise the recognition of an appropriate seizure pattern and the electroencephalographic evidence of a focal discharge in a patient resistant to medical treatment. The recognition of an appropriate seizure pattern is still of the utmost importance, notwithstanding the great value of abnormal electrical records. It is doubtful whether the wide variety of seizure manifestations has ever been more accurately and more fully described than by Hughlings Jackson and also by Gowers (1892) and this applies in particular to that variety of seizure which is now often termed temporal lobe epilepsy. In recent years interest has been focused particularly on the forms of mental disorder which may arise in persons suffering from this type of epilepsy. As in the passage quoted from Hughlings Jackson's writings, these disorders may be episodic and strictly related to a fit. But in other patients it seems that the mental disorder may persist and worsen without remission, rendering the subject unable to retain his place in the community. Such deterioration may not necessarily be permanent if the discharging and apparently disorganizing focus can be detected and removed, as the following two cases exemplify.

Case Histories

Case 1.—M. G., aged 18 years, was referred to Runwell Hospital from the Royal Eastern Counties Hospital because of bouts of violent uncontrollable behaviour and repeated attempts to abscond. He was the seventh child of healthy working-class parents. There is no family history of epilepsy. His birth was normal and he was breast fed for nine months. He began to walk and talk at about 14 months. As a child he was placid but active, easily managed, and there were no difficulties in toilet training.

At the age of 7 years he fell out of a tree and was momentarily unconscious. Then 15 months later he began to have fits which initially consisted of feeling giddy followed by a momentary lapse of consciousness but no falling, and during this period he would raise both arms above his head. This would occur up to seven times a day. Associated with this, a change in his personality occurred, for at school he started to become mischievous and " played-up " his teachers. Until this time school reports show that he was an average scholar. About 10 months after the onset of these minor fits, the character of his fits changed. They became more severe and falling and convulsive movements occurred. These turns were preceded by a well marked aura lasting up to two minutes, which enabled him to warn people near him that a fit was pending. The aura consisted of a fully formed musical tune which he felt he had heard a long time ago, but occasionally it consisted of the sound of bells, accompanied by giddiness. He was never able to describe the tune or to remember it after the attack. There were no known precipitating factors. Occasionally, by hard concentration, he was able to abort the fit. Following the aura, the head and trunk would turn to the right and the right arm would flex before the onset of clonic movements in all four limbs. Several such fits were observed in this hospital. The onset of these fits was accompanied by a rapid deterioration in his behaviour, and at the age of 11 years he was admitted to an epileptic colony for 16 months. After this time his removal was requested because of his antisocial behaviour and frequent attempts to abscond. His I.Q. was 81 (revised Stanford-Binet scale form L) at this time. There followed a period at home in which his behaviour

deteriorated still further and fits occurred unchecked by medical treatment ; he was certified as a mental defective at the age of 14 years and admitted to the Royal Eastern Counties Hospital. While in this hospital he had episodes of bizarre behaviour in which he would climb on lockers and wander off without subsequent recollection and if restrained would become violent and destructive.

Physical examination at Runwell Hospital revealed a healthy youth who showed a mild right hemiatrophy with a right involuntary facial weakness, especially when he smiled. His speech was slurred and delivered in a whining, ingratiating way. There was also a right extensor plantar response. Mental examination revealed a rather simple youth who smiled readily in a fatuous way. He constantly importuned everyone for cigarettes or food and at other times demanded that they should listen to simple rhymes he had made up. Anyone would act as a trigger for him to demand in a whining tone, " Give us a fag, sir ". This constant whining patter was a source of annoyance to other patients as was the repetition of jingling rhymes.

" None of these won't let me give him a saccharine
Because they think it might make him dream
And if he dream
He might turn green
So he don't look clean
And so he might never see the Queen."

His emotional behaviour in every way was like that of a child of 7, for he sulked readily. If no one listened to the verses he became pettishly annoyed. Slight praise would send him jumping for joy. He entertained vaguely hostile ideas against the nursing staff who, he felt, watched him unnecessarily closely and curtailed his activities. He was inquisitive, constantly interfered with people, and never seemed to learn from his rebuffs. He was correctly orientated, fairly well informed about current events, and performed serial sevens promptly and accurately. For long periods he would occupy himself painting designs with great thoroughness. He was able to write a few simple words, but spelling was poor. His vocabulary was surprisingly good. Psychometric examination gave him on the Wechsler-Bellevue a verbal I.Q. of 63, a performance I.Q. of 48, making a full I.Q. of 51. On Raven's Progressive Matrices he obtained 29 correct solutions, being Grade IV. An air encephalogram revealed dilatation of the inferior horn of the left lateral ventricle. Electroencephalographic examination of August 6, 1952, revealed considerable high voltage dysrhythmic activity in the delta and theta groups from all areas, but greater on the left side. Fronto-temporally the abnormality was very much greater on the left side than the right and was focal over the left anterior temporal region (Fig. 1). The delta activity here was frequently associated with both slow and fast spikes which were likewise focal. Posteriorly an alpha rhythm at 9 c/s. was discernible, responding to opening the eyes.

The above behaviour was frequently punctuated by that of a different sort in which he became excessively hostile, withdrawn from people and refusing food. The

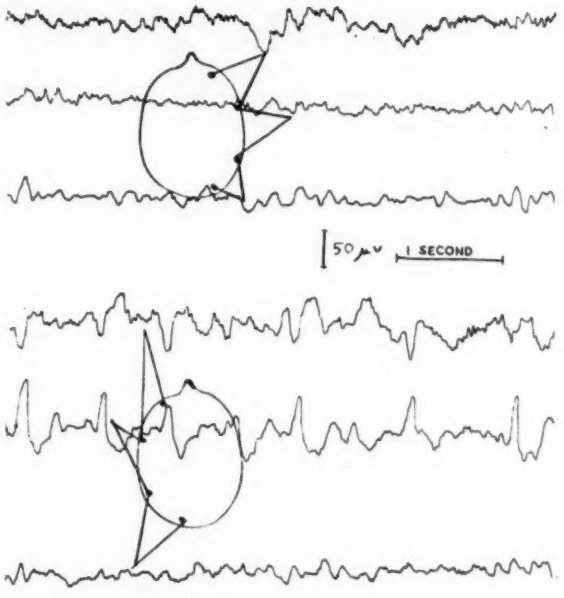

FIG. 1.—Case 1 : E.E.G. reveals left anterior temporal sharp wave focus.

slightest provocation would send him into a violently destructive rage. During this period, which would last up to 48 hours, he was confused and disorientated. He had obvious difficulty in finding words and when attempting to speak was unable to give any clear account of himself. His mouth would frequently move but no sound emerged. Afterwards he had little or no memory for these periods. During one such turn his E.E.G. revealed continuous high voltage 2½ c/s. and 5 c/s. activity over the whole cortex (Fig. 2). These episodes were considered to be prolonged automatisms.

On December 3, 1952, left temporal lobectomy was performed, as the usual anti-epileptic medication in various combinations seemed in no way to control either his fits or behaviour, for even on heavy medication he was having up to 24 fits per month, often in bouts of three or four per day, in addition to his periods of prolonged automatism which might occur weekly.

The operation was carried out under local anaesthesia, following premedication with morphia, a minimal dose of pentothal being administered for breaking the bone flap (Dr. Waterfall). The surface of the brain was of normal appearance. Unfortunately, electrocorticography as planned could not be undertaken. The inferior extremity of the precentral gyrus was identified by electrical stimulation (sine-wave, 2 volts for two seconds) but no responses could be evoked from the exposed surface of the temporal lobe. A formal partial lobectomy was carried out, the posterior line of section traversing the lobe approximately along the vein of Labbé, the plane of its upper (Sylvian) limit lying 5 cm. and its inferior limit 7 cm., respectively, behind the tip of the temporal pole. The resection included the uncus, and as much of the hippocampal gyrus as lay anterior to the plane of the section. The insula was left intact.

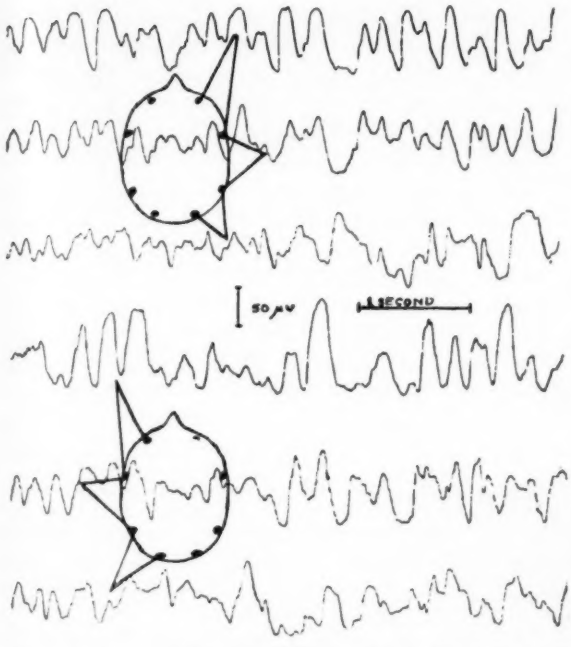

FIG. 2.—Case 1 : electroencephalogram taken during a period of prolonged automatism showing diffuse high voltage at 2½ c/s. and 5 c/s. activity.

Pathology.—Dr. J. A. N. Corsellis reported as follows : The weight of the fixed specimen (10% formalin) was 32 g. It measured 5 cm. antero-posteriorly and 5 cm. latero-medially (superior temporal gyrus to hippocampus).

The specimen consisted anteriorly of the intact temporal pole. More posteriorly it included the three temporal gyri (the upper surface of the superior temporal was largely missing), the fusiform, and the hippocampal gyri. Its medial border was formed by part of the amygdaloid nucleus, the wall of the inferior horn, and a small part of the hippocampal formation (Fig. 3).

FIG. 3.—The naked-eye appearance of the specimen cut coronally 2·5 cm. posterior to the temporal pole in Case 1.

Apart from much congestion and many small areas of recent haemorrhage no abnormality was seen either on the surface or after cutting the brain.

The specimen was cut into three coronal blocks and sections were examined from each level. The established abnormal histological findings, i.e., present before operation, were those of a moderately severe sub-pial glial fibrosis extending down into the second cortical layer (Fig. 4). There was also a marked increase of astrocytes in the white matter and a fine glial fibrosis. A fragment of the hippocampal formation was present but no dentate gyrus. This fragment included a part of the Sommer section (H 1) where the layer of pyramidal nerve cells was present but, as elsewhere in the cortex, many of these were shrunken and darkly stained, and related probably to the operation. The glial changes, although patchy, were of about equal severity in all areas examined and no localized lesion of any kind was found.

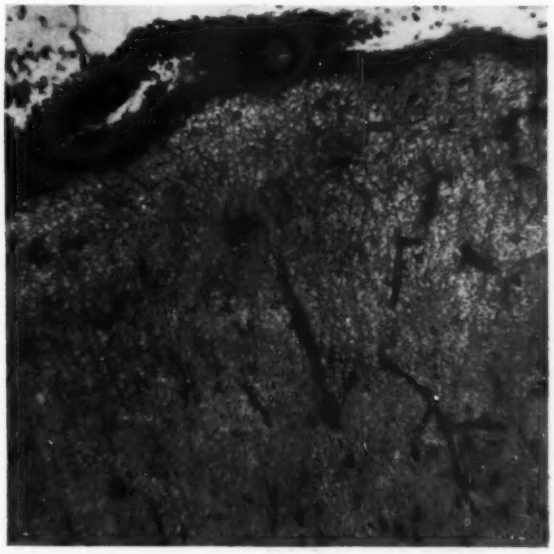

FIG. 4.—A fairly dense sub-pial glial fibrosis, also penetrating into the cortex in Case 1. Mallory's P.T.A.H. × 184.

Post-operative Course.—There have been no fits since the operation 17 months ago. Immediately after operation the patient was hypersomnolent and it was impossible to arouse him by the usual method of shaking. He would wake at meal times but was fed with difficulty. However, after 14 days this gradually passed off. When he was up and about a noticeable change in his behaviour was apparent ; he was quieter and more contented. He lost all his previous persistent importuning attitudes and was able to attend occupational therapy where he worked well. In addition he started to learn to read, which previously he was unable to do except for simple words. All his cravings for cigarettes and food vanished and he rapidly lost his habit of repeating childish rhymes and quips. Speech, however, lost its natural cadence and each word was delivered with the same emphasis. He became alert, well behaved, and began to take a pride in his appearance. Eight months ago he was let

out on licence and since then has been diligent at home. His mother is delighted with the change in him. Of great interest is that following operation he has grown rapidly in height. His mood has changed from that of a child to one of quiet stolidity. He occupies himself for long periods alone and is planning to become a gardener. His I.Q. has also shown a steady improvement (see Table). This case shows clearly how profoundly the

TABLE

PROGRESSIVE IMPROVEMENT OF INTELLECTUAL PERFORMANCE IN CASE 1

Test	29.11.52 (before operation)	2.1.53	8.2.54
Wechsler-Bellevue Scale :			
Verbal I.Q.	63	73	79
Performance I.Q. ..	48	65	74
Full scale I.Q. ..	51	66	75
Progressive matrices ..	29 correct results Grade IV	41 correct results Grade III	43 correct results Grade III

I.Q. will drop in epilepsy occurring early in life, for we have an early intelligence test obtained while he was in an epileptic colony when his behaviour and learning ability had already begun to deteriorate. It was then 81. Over the next few years his intelligence dropped progressively, until before operation it was 51. Since then it has shown a continual rise. The Progressive Matrices, which have perhaps the highest " g " saturation, show that his intelligence is now average. The Wechsler-Bellevue test does not to date confirm this great improvement, but the test is no doubt dependent on education and learning as well as intelligence.

The E.E.G. a month after operation revealed a right temporal focus of sharp waves by phase reversal, but this had vanished three weeks later when the record was normal except for some flattening and low-voltage slow activity over the left temporal region (Fig. 5). However, 13 months later the E.E.G. revealed a right slow frequency posterior temporal focus of 5 to 7 c/s. activity which responded rapidly to opening the eyes (Fig. 6). This type of response has been described by Hill (1952) as a maturational phenomenon occurring normally in children and only of pathological significance if persisting into adult life. The great interest in this is that not only has the focus appeared but its appearance has coincided with a rapid increase in physical growth and a rapid maturation of his personality from that of a child to one of an adult. Its presence may well indicate the possibility of still further improvement in this youth. It would seem that a frequently discharging lesion of an area of the brain has, as Krynauw (1950) suggested, profoundly altered the function of normal brain. Its removal has allowed maturation to proceed and accompany-

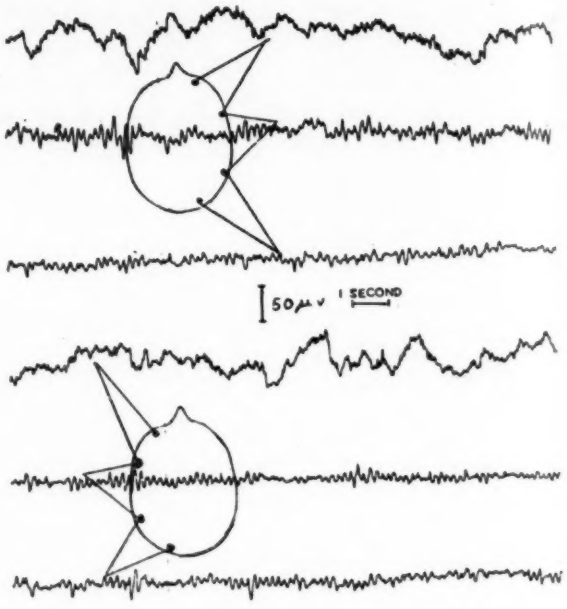

FIG. 5.—Case 1 : E.E.G. post-operatively appearing normal apart from low-voltage slow activity over left temporal region.

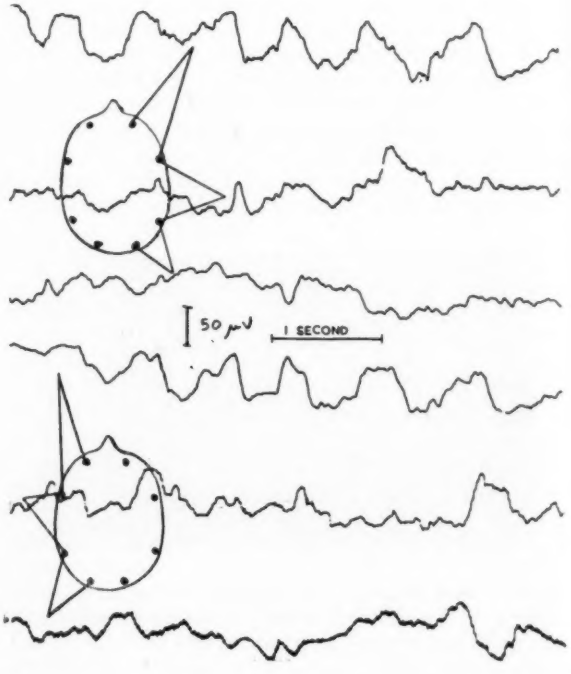

FIG. 6.—Case 1 : E.E.G. 15 months post-operatively showing right posterior temporal slow wave focus responding to opening of the eyes.

ing this there has been a generalized increase of active growth affecting body and personality.

The hypersomnolence is an unusual feature. Gibbs, Gibbs, and Fuster (1948) claim that it is common amongst patients with temporal lobe epilepsy, but this has not been our experience. However, Poirier (1952) in attempting to obtain Klüver and Bucy's syndrome in monkeys by producing minimal bilateral temporal lobe lesions, obtained instead hypersomnolence in monkey No. 5. This monkey was in a state resembling those asleep following hypothalamic lesions. Microscopic studies, however, showed that the lesions did not involve the hypothalamus, but chiefly the medial and basal portions of the temporal lobe, especially in the amygdaloid area.

Case 2.—H. G. R., aged 20 years, was referred to Runwell Hospital from the Royal Eastern Counties Hospital because of aggressive outbursts and degraded behaviour. The patient was the fourth sibling of seven children, born of working-class parents. There is no family history of epilepsy but a maternal great-aunt was an imbecile. His birth was normal and he was breast fed. He was always a contented child, walked at 11 months and began to talk a few months later. At the age of 5 years he began to have temper tantrums and bit his nails. He attended school until the age of 15 years. Reports state that he was rather backward but could do better if he tried. However, he learnt to read and write. On leaving school he was apprenticed to a carpenter and was apparently a willing worker and well liked. He was particularly attached to his mother and frequently bought her little presents. He was polite and well mannered. He used to save his money and only smoked occasionally.

When about 15½ years of age, he sustained a head injury and four months after this had his first "black-out". He would suddenly stare vacantly ahead for a minute and afterwards became confused and restless. When he had returned to normal he would remember nothing of the episode. Once started, the fits rapidly increased in number in spite of medication. Because of the repeated attacks of confusion, he was kept in the house. However, he did not understand the reason and resented the confinement and became moody and difficult. At this period he developed an intense craving for cigarettes and started to look everywhere for them. Because of this craving he began to steal small sums of money and whenever he managed to get out of the house he would also steal from neighbours and shopkeepers in order to satisfy his desire for a smoke. Eventually, repeated larceny brought him to court at the age of 16 years, and from a remand home he was transferred to a mental hospital as a voluntary patient, but because of frequent wandering he was certified as a mental defective. Major fits are said to have occurred but no description was obtained.

In the Royal Eastern Counties Hospital his turns continued unabated and a striking deterioration in his behaviour resulted. He was described as noisy and garrulous, filthy in his habits, even eating his own excreta. He had an intense craving for cigarettes. He masturbated freely. At times he became impulsive and violent towards other patients. His I.Q. in 1950 was 63 on Terman-Merrill form L.

While in Runwell Hospital, before operation, he had numerous turns in which he would go stiff, stare into space for half a minute and then become more confused than usual for 10 minutes. There was no chance of missing a fit, for he always ran to a nurse pressing his own hand against his head and moaning. Following lobectomy he was able to elaborate on his aura ; it was an intense, agonizing pain of sudden onset in the centre of his head. He further added that if the aura occurred at night it always did so at the end of a particular dream, in which he finds himself snatching his sister's handbag out of her hand and then running off. As he ran away the severe headache occurred. During the day no thought or idea was associated with the cephalgia. A constant form of automatism was rummaging through the nearest person's pockets, or banging his head against the nearest wall at the beginning of his confusion.

Physical examination revealed a healthy youth who looked much younger than his years. Speech was slurred, probably due to barbiturates, but there was no nystagmus. Apart from gross unsteadiness while standing on the left leg, there were no abnormal physical signs in the central nervous system.

Mental examination revealed a confused youth who could give little account of himself. His voice was loud and whining and his conversation was broken continuously by demands for cigarettes. He was unable to pursue any topic, for after a few words a fresh demand for cigarettes would arise and he would forget what he had said previously. In addition, long pauses would occur, and often the same word would be repeated a number of times. He frequently took hold of people's hands and put them in his mouth. In fact most interviews would begin with this procedure and it appeared to be his method of identification. However, he appeared to obtain great pleasure by formulating very simple, childish conundrums and was delighted if he caught ar one out. He was excessively inquisitive and wanted to pry into everyone's acts ; whatever they were doing he wanted to do. Repeated rebuffs had no effect on him and often he had to be isolated to protect him from more impulsive patients who became more than irate as he fingered all their belongings. He was never silent, but kept up a constant loud, whining speech. He was never still, would wander all over the wards trying to pilfer cigarettes, and never sat or occupied himself. His habits were degraded. All objects were correctly named. He was able to read a little and also write a few simple words. He was able to repeat only four digits forward and none backward, and his grasp of general knowledge was equally poor.

Psychometric testing gave him on the Wechsler-Bellevue test a performance I.Q. of 63. An air encephalogram revealed normal ventricles. An E.E.G. revealed high voltage, continuous slow activity at 1 to 5 c/s.

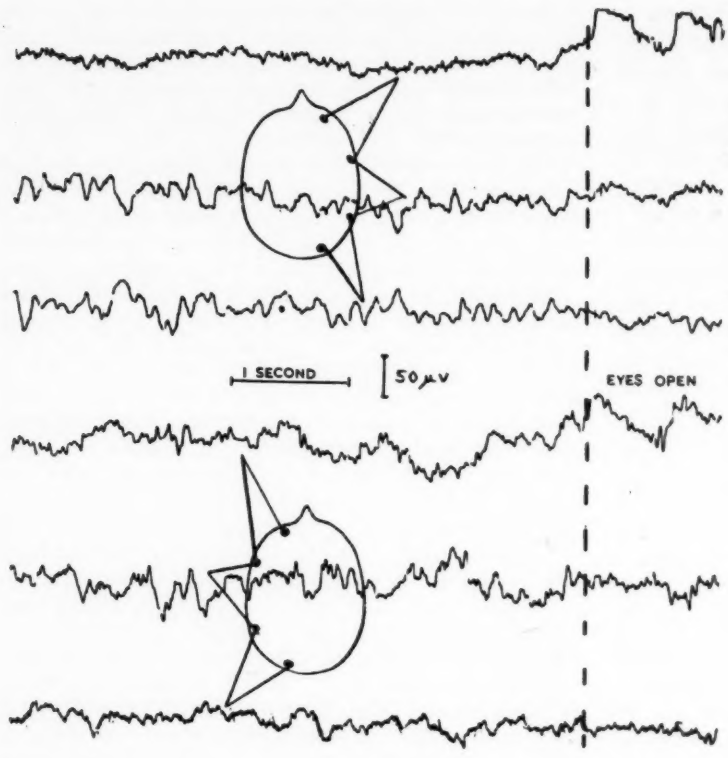

FIG. 7.—Case 2: E.E.G. before operation showing generalized mixed slow activity.

which was greater over the right cerebral hemisphere (Fig. 7). Sphenoidal electrodes revealed an almost continuously firing right basal sharp wave focus (Fig. 8) and this was frequently associated with firing from the left base which appeared to be secondary to that on the right. Throughout, the cortical activity remained unchanged at 1½ to 3 c/s.

On December 17, 1953, right temporal lobectomy was performed under light general anaesthesia (gas, oxygen, and pentothal, Dr. Stride). The surface of the brain appeared normal. Electrocorticography revealed a considerable abnormality, particularly from the anterior part of the lobe, and there was evidence that the discharges were arising anteriorly—from an area hidden under the bone—and spreading backwards. The record included high voltage delta and theta activity, random spikes and sharp waves, and at times runs of spikes at beta frequency. Cortical stimulation (sine-wave, 2 and 4 volts for two seconds) produced no change in the electrocorticograph. Formal lobectomy was carried out, the posterior plane of resection lying 5 cm. behind the tip of the temporal pole, and including the uncus and as much of the hippocampal gyrus as lay anterior to that plane. The brain tissue appeared tougher than normal, and this was particularly the case in respect of the uncus and hippocampal gyrus, where the leptomeninges were also thickened and tough. The medial part of the uncus extended further over the free edge of the tentorium than is usual in a case with no tumour. The insula was preserved. Electrocorticographic records taken at the end of the operation revealed a marked reduction of all activity from the surrounding brain, there being only a very few low-voltage random spikes.

Pathology.—Dr. J. A. N. Corsellis reported as follows: The weight of the fixed specimen was 45 g. It measured 5 cm. antero-posteriorly and 6 cm. latero-medially.

The anatomical limits of the specimen generally resembled those in the first case although only the infero-lateral edge of the inferior horn was present and no hippocampal formation or amygdaloid nucleus was identified.

No macroscopic abnormality was seen (Fig. 9) but the fixed tissue felt unusually tough on section.

Glial changes similar in distribution and intensity to those in Case 1 were present. In the white matter the gliosis was more marked. No localized lesion was found.

Post-operative Course.—Since the operation four months ago there have been no fits. For the first week the patient maintained the same childish attitude to life, and then started to improve. The improvement has been

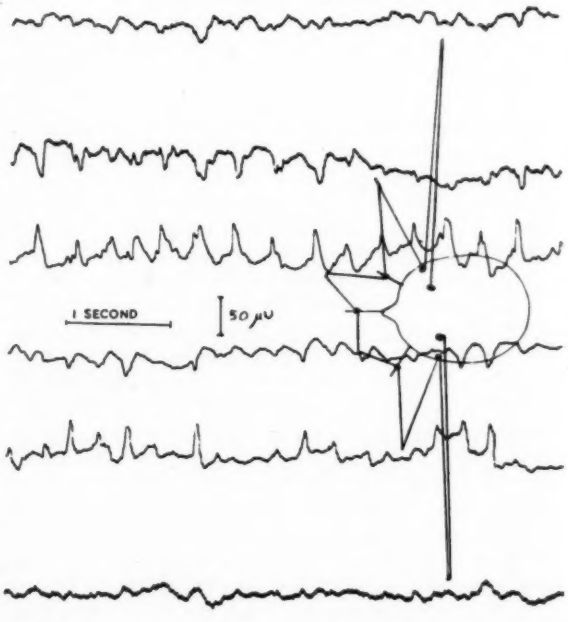

FIG. 8.—Case 2: sphenoidal leads taken at the same time as Fig. 5 showing well marked bilateral, frequently firing foci, right greater than left.

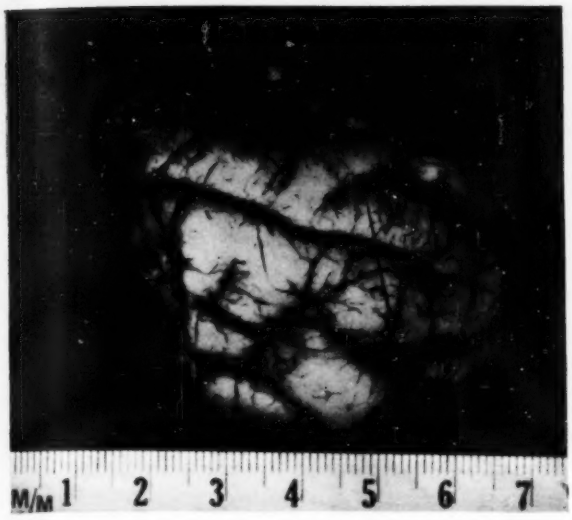

FIG. 9.—Lateral view of the portion of temporal lobe removed with the superior temporal gyrus uppermost and the pole to the right in Case 2.

rapid. He is now able to hold a conversation without losing his train of thought. Perseveration of ideas and words has vanished. He is no longer meddlesome, keeps very much to himself, and is able to occupy himself with simple woodwork. He is polite and takes some pride in his appearance. His voice, however, is monotonous and has lost its normal cadence. He is able to name objects correctly and read and write to a small extent. On confrontation there is no visual field defect. Apart from some low-voltage theta activity at 4 to 6 c/s. in the right temporal region, the E.E.G. taken one month post-operatively shows a normal record (Fig. 10). At about this time he was taken round the hospital to the wards in which he had been first, but had no recollection of them, the nurses, or the patients. He could give no account of his time in hospital and did not know how long he had been there.

Six weeks after operation he spontaneously remarked that one of us (D. W. L.) was now of normal size. He was able to elaborate that when he first started to remember things after the operation, and to understand his whereabouts, he was surprised to find that everyone was excessively tall, and the outline indistinct. He could only focus on one thing at a time, everything else would vanish, but now, as he says, he can see near and far. Also, at this time, objects had lost their weight. An ashtray, a cigarette, and a table all felt light, and when he lifted them there was no difference between them; but now " the table is heavy ". Voices also, especially in the morning, were very loud and grated. This he exemplified by screwing up his face and putting his hands over his ears.

One month after operation the full scale I.Q., as estimated by the Wechsler-Bellevue test, had risen to 69, verbal I.Q. 70, performance I.Q. 73. The performance part of the test showed a gain of 10 points. This test was carried out at the time when he still had the perceptual disturbance described above and is probably not a full guide to his intellectual improvement. Raven's Progressive Matrices were not done before operation, but when given nine weeks afterwards he obtained a score of 28, Grade IV−, which in this case corresponds closely to the Wechsler-Bellevue I.Q.

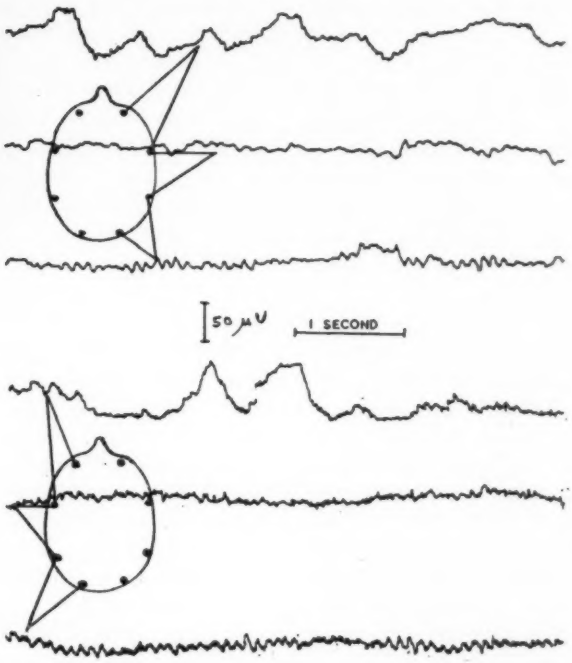

FIG. 10.—Case 2: one month post-operatively showing normal record with return of alpha rhythm.

Discussion

The clinical records of these two youths have much in common. Their birth and early years were normal, but after head injuries fits developed leading to a rapid deterioration in all spheres of behaviour. This deterioration eventually led to certification as mental defectives.

In both cases the fits were of the temporal lobe type, with well marked aura and not infrequent post-epileptic automatism.

Their behaviour showed the most remarkable deviation from normal, especially in the second case. Both showed excessive " orality ", constantly demanding cigarettes and talking incessantly. They obtained great enjoyment from making simple quips, and the first patient constantly recited home-made childish rhymes. They were both extremely restless and meddlesome, interfering continually with other people's activities, and failed to learn from their rebuffs. In fact, H. G. R. often had to be separated from other patients for his own

protection. This patient, in addition to the above symptoms, showed increased sexual activity as judged by masturbation. A peculiar form of oral recognition, in which objects, and especially people, were identified, was also present. The person's hand under review would be taken to the mouth. At no time did he ever attempt to bite. In addition, there was gross impairment of memory, for he was unable to recall post-operatively his previous two months' stay in this hospital. This was associated with perseveration of speech which commonly occurs in organic deterioration with loss of memory. This memory failure may be related to the frequently firing focus and secondary disorganization of the cortical electrical activity. The operation has resulted in an improvement of his ability to remember, for now he can recall events that have happened post-operatively. The perseveration of speech has also been abolished. After the return of normal recall he was able to describe a peculiar distortion of objects in which they appeared elongated and indistinct, and at the same time appeared to have lost their weight. It was impossible to determine how long this disturbance had been present because the loss of recent memory extended for an unknown period into his past. The perceptual distortion is of a type that occurs after mescaline intoxication. It is a most unusual response and is unlikely to be the result of a physical change in the brain as a result of surgery, because temporal lobectomy is frequently carried out for other lesions and this response has not been encountered before. It is most likely due to either a perceptual disturbance or based on lack of memory engrams by which judgment and comparisons are made. The latter cause is perhaps ruled out by the fact that he was able to conclude spontaneously that objects were now of normal dimensions and it is known that his memory up until at least 15 years of age was relatively intact, but more important still is the fact that he was able to name common objects correctly in spite of the distortion. It would seem therefore that it is a perceptual disturbance and this is apparently the basis of his peculiar inability to recognize people, except perhaps by oral sensations which are both physiologically and psychologically the earliest developed and probably form the most deeply entrenched engrams of all.

These symptoms are strongly reminiscent of the syndrome described by Klüver and Bucy (1939) which developed in monkeys subjected to bilateral anterior temporal lobectomy. These animals showed (1) " psychic blindness " in which they appeared unable to recognize objects on a visual basis alone ; (2) strong oral tendencies in which all objects were examined by mouth or nose ; (3) " hypermetamorphosis " which is used to describe a tendency for the monkeys to react to all objects as if under an " irresistible " impulse, thus showing an excessive tendency to react and take notice of everything in their visual field ; (4) emotional changes in which the monkeys lose both their sense of fear and ready reaction to anger ; and (5) increased sexual activity.

Comparing the above symptoms with those present in our two patients, it will be seen that they are not dissimilar. However, an apparent paradox arises when it is realized that our patients exhibited the above symptomatology when the temporal lobes were intact, and their behaviour was relieved by the removal of a temporal lobe. This may be explained by the fact that the diseased lobe was frequently firing, especially in the second case, and caused the opposite lobe to fire synchronously and almost as frequently. As Jackson (1931b) pointed out : " Strong epileptic discharges paralyse the nervous centre (or much of it) in which they begin and through which they spread." Hence, this is equivalent to the functional loss of both temporal lobes. Besides the discharging foci, the electrical activity of the whole cortex was completely disorganized. It is more than probable that because of this the highest symbolic thinking by which man is distinguished from primates was so grossly disturbed that the ground for such a syndrome to develop was readily available. After operation the remaining lobe returned to a potentially normal state, as shown by the cortical electrical activity on the E.E.G., and so allowed normal behaviour to be established.

As a result of the operation both had monotonous voices with the loss of natural cadence, although in each case a lobe from a different side was removed and they were both right-handed. This monotonous voice was not due to lack of affect, for this was normal. In fact the monotony of speech was present when they were discussing interesting topics. It would seem to be a disturbance of an integral part of speech, or at least its development, for this disturbance has not been observed in adult patients whose fits started in later life. The natural cadence of the spoken word depends on the harmonious blending of the requisite idea and the emotion behind it. In these youths their emotional development was perhaps even more disturbed than their intelligence, and so this aspect of speech had a poor chance of developing.

In both cases temporal lobectomy of the more severely disturbed side has produced to date complete abolition of fits and a profound improvement in personality. Whether this will be permanent it

is as yet too soon to say. However, it has given them a chance which would have been denied them without surgery.

Summary

Two cases of temporal lobe epilepsy, beginning in early life as a result of head injury, are described.

Attention is drawn to the associated disturbance in behaviour and its similarity to the Klüver and Bucy syndrome.

Temporal lobectomy was performed with amelioration of behaviour and a steady improvement in intelligence.

In one case, as a result of surgery, a maturational focus appeared in the E.E.G. and was associated with increased physical growth and emotional maturity.

As a result of surgery a monotonous voice developed and a possible explanation is offered.

We wish to thank Dr. R. M. Bates, Physician Superintendent of the Royal Eastern Counties Hospital, for referring the cases to us, and Dr. R. Ström-Olsen and Dr. D. Hill for helpful criticism.

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PATHOLOGICAL FINDINGS IN TEMPORAL LOBE EPILEPSY

BY

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Temporal lobe epilepsy, similarly to focal epilepsy arising elsewhere in the brain, can result from a wide variety of lesions that may involve the temporal lobe. Some of these may be of sufficient size, as for example most tumours, cirsoid angiomas, porencephalic cysts, and the scars of penetrating head injuries, so that their presence can usually be revealed by the appropriate clinical and radiological examinations. More often, however, the neurological examination is negative (apart from electroencephalography) and cerebral arteriography and encephalography do not disclose any such tangible abnormality. The underlying pathological basis then is a matter for speculation and conjecture. For more than a century it has been known that sclerosis of Ammon's horn (hippocampus) is a finding frequently observed at necropsy in the brains of chronic epileptics. It was noted by Spielmeyer (1927) in 80% of 126 epileptic brains, but until recently no attempt had been made to relate this particular lesion to the manifestations of temporal lobe epilepsy.

Our interest in this subject was specially aroused by the paper of Penfield and his collaborators (Earle, Baldwin, and Penfield, 1953) claiming that " incisural sclerosis " was the most common cause of temporal lobe epilepsy. It had been found by them in 100 out of 157 patients (63%) submitted to operation. The extent of this sclerosis ranged from involvement of a single gyrus to involvement of the entire temporal lobe, but the mesial and inferior portions of the lobe (uncus, hippocampal gyrus) and first temporal gyrus were the areas most frequently involved. However, they did not specify whether the sclerosis of the hippocampal gyrus also extended to Ammon's horn. They further claimed that this incisural sclerosis is caused exclusively by herniation of the temporal lobe into the tentorial opening during the head moulding of parturition. This herniation, they held, occurs at a time when the temporal lobe is poorly developed and more susceptible to damage through compression of the anterior choroidal, posterior cerebral, and middle cerebral arteries against the tentorial edge with consequent local anoxia. This is a challenging hypothesis that runs counter to the widely accepted views that sclerosis of Ammon's horn, when it occurs in epileptics, is secondary to severe major epileptic seizures. In their remaining 57 cases Penfield and his associates found a post-natal pathology, usually in the form of tumours or the sequelae of head injury or infection.

Case Material

We have therefore analysed the biopsy findings in 18 cases of temporal lobe epilepsy treated by temporal lobectomy in the Guy's-Maudsley Neurosurgical Unit between May, 1951, and July, 1953. Each case was one of intractable epilepsy, usually with a range of seizures of minor, amnesic, and grand mal types (Falconer, 1954), in which the electroencephalographic studies had disclosed an epileptic focus confined to or largely predominant in one temporal lobe, while the clinical and neuroradiological examinations had not revealed a tangible structural lesion. Many of the patients suffered also from an associated personality and behaviour disorder. The clinical, operative, and electroencephalographic data in the first 14 of these cases have already been reviewed by Hill, Falconer, and Pampiglione (1953). Several other cases of temporal lobe epilepsy due to large structural lesions, such as readily recognizable tumours, porencephalic cysts, and angiomas, were also operated on during the same period, but these were excluded as the operative intervention in them was limited to an excision of the lesion, whereas the cases in the present series were treated by an excision of the greater part of the temporal lobe.

Most of our biopsy specimens contained the anterior half to two-thirds of the temporal lobe, usually from the middle temporal convolution laterally to the hippocampal gyrus medially. The first temporal convolution, if it was included at all, was usually incomplete ; the Ammon's horn was occasionally missing, particularly in the earlier

specimens. Whenever there was no macroscopically obvious focal abnormality, the blocks into which the specimen was divided were embedded in celloidin and cut in serial sections. Usually only a small amount of tissue was left for the techniques applicable on frozen sections.

Histological investigations of biopsy specimens have their special difficulties. Nerve cells and fibres almost invariably show artefacts. Extravasations of blood and mechanical damage during the operation obscure the architecture. Moreover, some staining reactions, and in particular the glial fibre stains so important for the assessment of age and severity of a lesion, are seldom satisfactory. In this regard Mallory's phosphotungstic-acid-haematoxylin stain proved to be superior to Holzer's stain. We had to bear these difficulties constantly in mind in the interpretation of the lesions.

Histological Findings

Our case material on analysis proved to be divisible into two groups corresponding to those of the Montreal workers. The first group comprises four cases with small but macroscopically clear-cut circumscribed lesions. The second and larger group consists of cases in which such local lesions were absent, and in which the changes were essentially of a more diffuse and microscopic character.

Group 1 : Small, Macroscopic, Focal Lesions.—In three instances these proved to be small tumours, while the fourth case was one of traumatic cicatrix. One of the tumours was a small meningioma situated on the inferior surface a little behind the pole and extending for about 2 cm. within the fusiform gyrus (Fig. 1). The histological diagnosis in this case was a surprise because there had been an antecedent head injury, and at operation the case was considered one of traumatic meningo-cortical cicatrix. The two other tumour cases have already been reported by Falconer, Pond, Meyer, and Woolf (1953) and would come under the generic term of hamartomas. In these a small calcified lesion similar to what Penfield and Ward (1948) described as a " haemangioma calcificans " was found, in one instance occupying the temporal lobe inferior to the temporal horn, and in the other the uncus and parts of the amygdaloid nucleus which are entirely obscured (Fig. 2). In the latter case the lesion was not noted at operation, and indeed its presence was not realized until the sections came to be examined. The well defined localization of the lesion in this case much resembles that in Hughlings Jackson's original case although the lesion there was a vascular one.

FIG. 1.—Small, well encapsulated meningioma indenting the fusiform gyrus. Van Gieson stain. × 5·5.

FIG. 2.—Haemangioma calcificans situated within the region of the uncus. Haematoxylin and eosin stain. ×8.

Group 2 : Non-circumscribed Microscopic Lesions.—This group contains 14 cases, and the relevant histological findings are set out in Table I under the headings of meningeal fibrosis, marginal gliosis, cortical atrophy, white matter gliosis, and Ammon's horn sclerosis. It will be seen that in each case some abnormality was noted although in greatly varying proportions. It can also be noted that frequently the skull on the side of the resected lobe was smaller than on the opposite side, suggesting a disturbance of development dating from early life, and that even more frequently the cerebral hemisphere on the operated side was small or showed other evidence of atrophy.

Meningeal Fibrosis.—Meningeal fibrosis was particularly marked in Cases 4, 5, and 6. The meningeal affection in these cases may possibly indicate trauma (neonatal or post-natal) or infection. There were some scanty lymphocytic and leucocytic infiltrations in the meninges of Cases 4 and 5, but their aetiological significance is doubtful in view of the long history in both cases.

FIG. 3.—Case 6 : marginal gliosis. Mallory's phosphotungstic acid-haematoxylin stain. × 300.

FIG. 4a.—Case 2 : cortical atrophy and white matter sclerosis. Nissl stain. × 3.

FIG. 4b.—Normal temporal lobe for comparison. Nissl stain. × 3.

FIG. 4c.—Case 2 : severe laminary nerve cell loss within the third layer. Dense gliosis of the white matter. Nissl stain. × 25.

FIG. 3

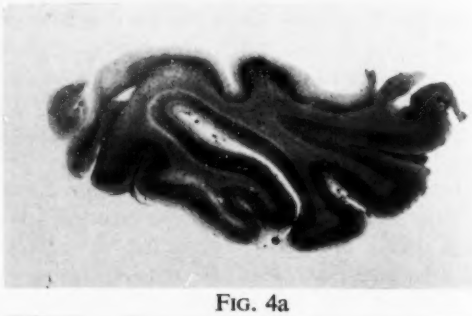


FIG. 4a

FIG. 4b

FIG. 4c

Marginal Gliosis.—Marginal gliosis of widely varying degree and extent was seen in every case. It was usually demonstrated fairly satisfactorily by Mallory's phosphotungstic-acid-haematoxylin stain as Fig. 3 indicates.

Cortical Atrophy.—Cortical atrophy was in several cases severe and generalized. Fig. 4a shows its degree in the anterior part of the temporal region near the pole in Case 2 in comparison with the corresponding region in a normal brain (Fig. 4b). A higher magnification (Fig. 4c) shows a generally thin cortex with the neuronal loss and glial overgrowth being particularly marked in layer 3 and, less often, in layer 2. This illustration compares well with figures 64 and 65 of Scholz (1951) in which he demonstrates laminary atrophy in post-epileptic lesions. Quite often the laminary atrophy was more localized and was found with particular frequency in the depth of the sulci, e.g., around the collateral sulcus (Fig. 5).

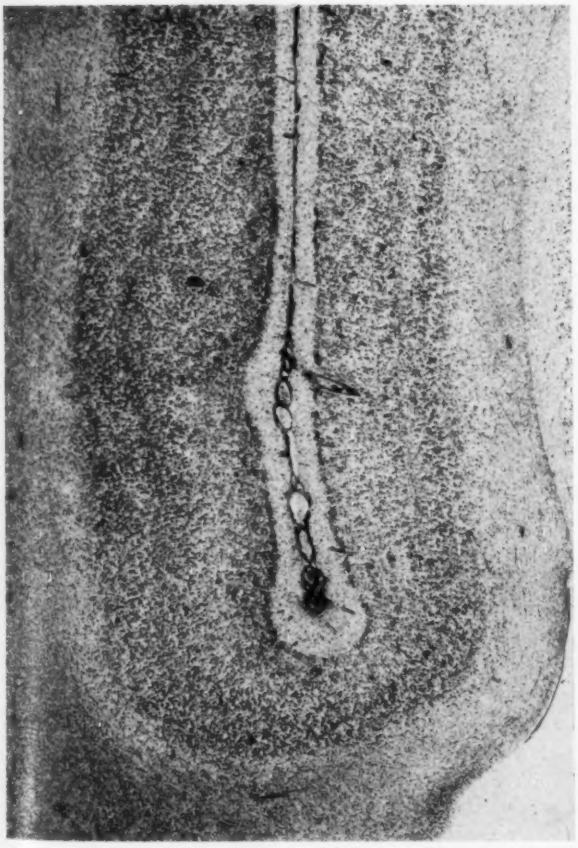


FIG. 5.—Case 14 : laminary atrophy of the third layer around the collateral sulcus and dense gliosis of the white matter. Nissl stain. × 13.

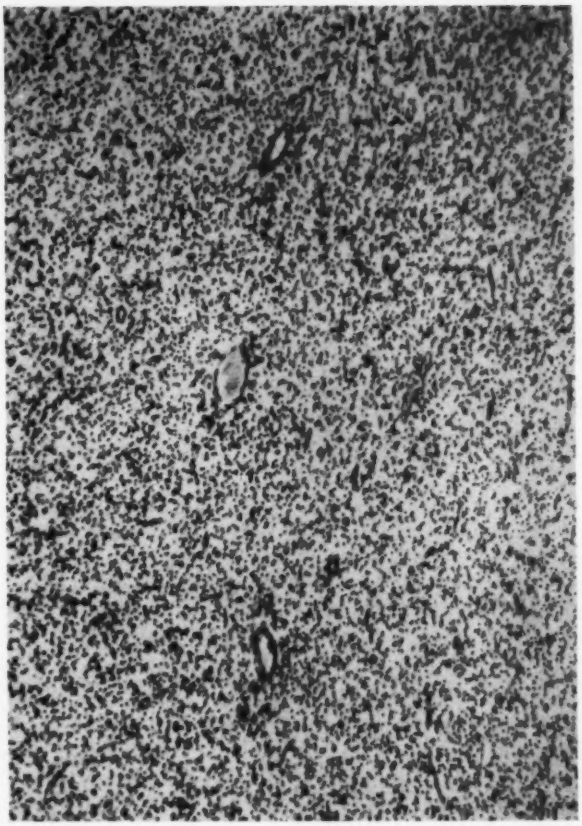


FIG. 6.—Case 10 : severe gliosis in the white matter of the hippocampal gyrus. Nissl stain. × 68.

Glial Sclerosis of White Matter.—Glial sclerosis of the white matter often accompanied the cortical atrophy, but in at least two cases it was more marked than the changes in the cortex. It was usually densest in the vicinity of the temporal horn and in the hippocampal gyrus (Figs. 5 and 6). Owing to the failure of glial fibre stains conclusions had to be drawn from the number of oligodendroglial cells and astrocytes in Nissl-stained slides. In none of the 14 cases of this group was there any appreciable demyelination, a fact of some interest since it renders a measles encephalitis, which as a rule is of the demyelinizing post-vaccinal type, unlikely as a cause.

Sclerosis of Ammon's Horn.—Fig. 7 illustrates the sclerosis of Ammon's horn, as found in Cases 10 and 3, compared with a normal hippocampus. In Case 10 (Figs. 7b and c) there was sclerosis of the Sommer sector (h1) and endplate (h3–h5) which also showed well after Holzer staining. (This patient died and these sections were taken after death from the unoperated hemisphere ; there was

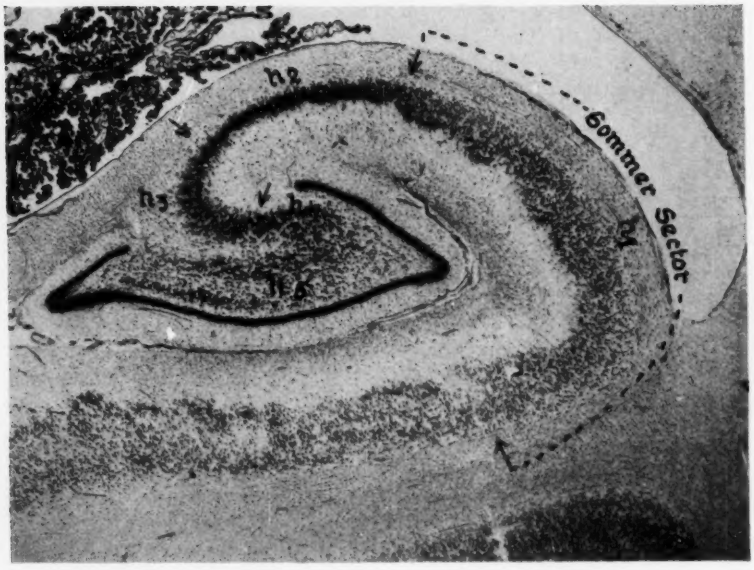


FIG. 7a

FIG. 7b

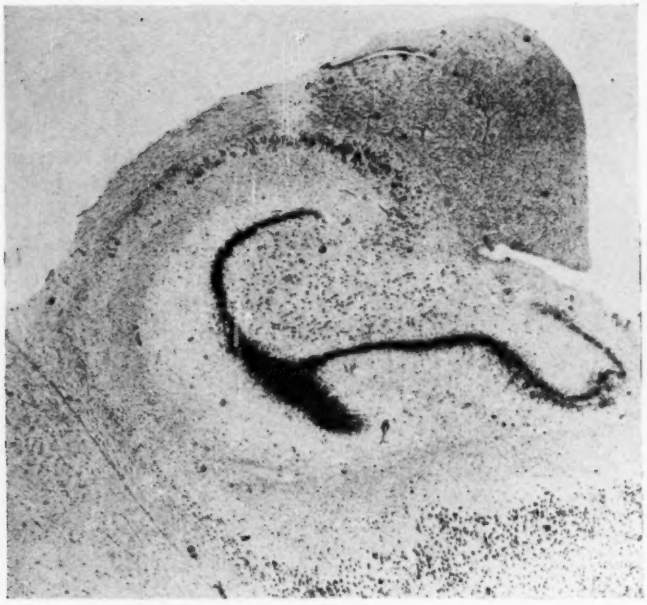


FIG. 7a.—Normal Ammon's horn. Nissl stain. × 10.

FIG. 7b.—Case 10 : Ammon's horn sclerosis in Sommer sector (h1) and end-plate (h3–5). Nissl stain. × 10.

FIG. 7c.—Case 10 : the same as Fig. 7b stained for glial fibres.—Holzer stain. × 10.

FIG. 7d.—Case 3 : complete sclerosis and severe shrinkage of all sectors of Ammon's horn. Nissl stain. × 10.

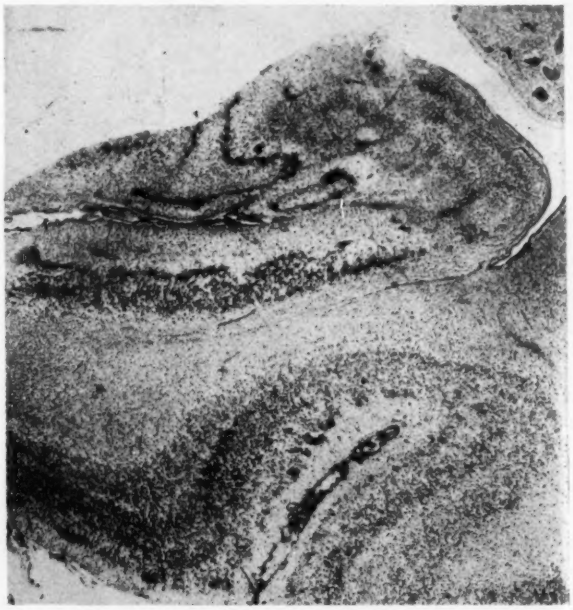


FIG. 7d

no sclerosis of Ammon's horn in the biopsy specimen.) Relatively little shrinkage was present compared with the much severer shrinkage in Case 3 (Fig. 7d). In Case 10 the sclerosis of Ammon's horn was not associated with cortical atrophy, whereas in Case 3 it was part of a severe atrophy of all available temporal convolutions.

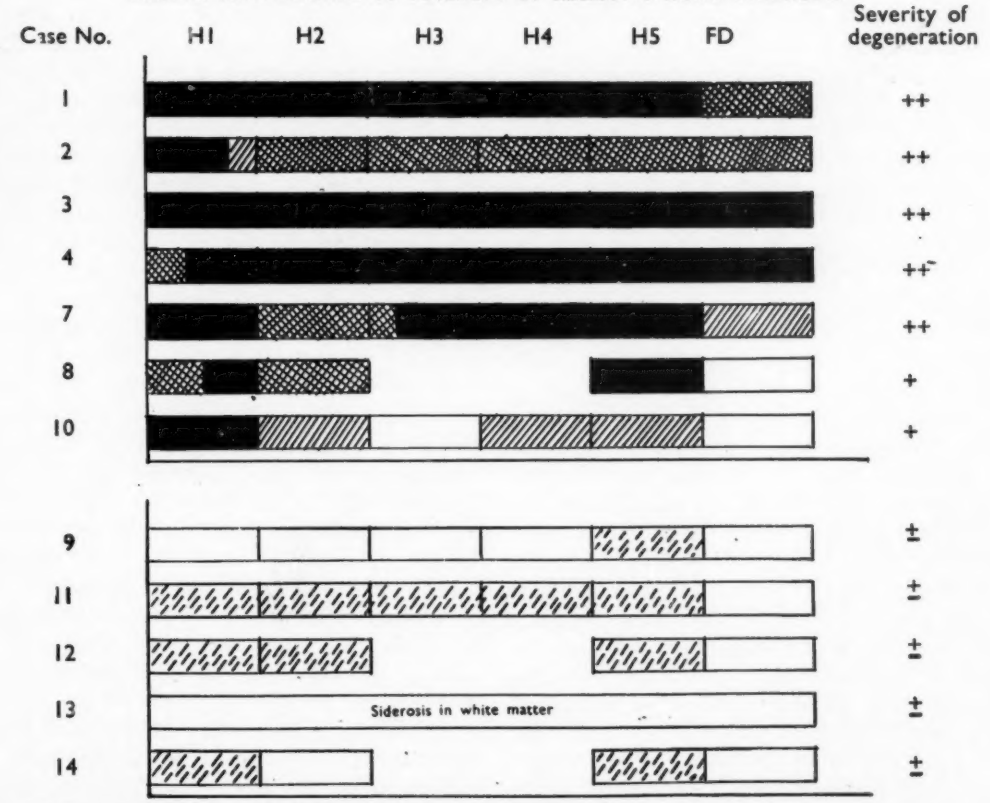
Table I gives the exact extent of the hippocampal lesion in the 12 cases in which this could be determined. It will be seen that a definite Ammon's horn sclerosis was present in seven cases although to a varying degree. In four further cases, although there was no appreciable loss of nerve cells in any sector, the glial cells were definitely increased in number. We have recorded this latter change as of uncertain significance (±). In the remaining case (Case 13) excessive siderosis (pseudocalcium) was observed in blood vessel walls. In two cases (5 and 6) no tissue of Ammon's horn was available for investigation.

Discussion

Some pathological change was thus observed in every case, while the post-operative follow-up studies at periods ranging from one to three years show that most cases have been strikingly benefited by removal of the diseased temporal lobe. The degree of improvement was particularly striking in those cases in which sclerosis of Ammon's horn was found. In only three instances was the therapeutic result not definitely beneficial. One patient, Case 10, died eight days after operation. Two others, Cases 9 and 14, were only slightly improved as regards the frequency and severity of their fits, and not at all as regards their personalities. In both of these there was evidence of involvement of the remaining temporal lobe as well. In Case 9 the pre-operative radiographs showed that the hemicranium and cerebral hemisphere on the unoperated side were smaller than on the operated side, while post-operatively the E.E.G.s have shown a pronounced epileptic focus on the unoperated side. Again in Case 14 the pre-operative radiographs gave evidence of a bilateral disturbance, as did the E.E.G.s.

The fact that following temporal lobectomy the clinical features were so frequently improved strongly suggests that the pathological changes were

TABLE I
EXTENT AND DEGREE OF SEVERITY OF AMMON'S HORN SCLEROSIS



H1–5 correspond to Rose's subdivision of the Ammon's horn, H1 being approximately the Sommer sector.
FD = fascia dentate.
Solid black indicates complete degeneration; cross hatching, single, and broken lines gradual decrease in severity.

somehow responsible for the epilepsy, which had improved as a consequence of their removal. This is in keeping with the general clinical observation that the mechanisms responsible for epilepsy are dependent not so much on the nature of the pathological change as on its site.

Several points of importance emerge from the presence of Ammon's horn sclerosis in our material. Its incidence (if we leave out uncertain cases) is no higher than has been reported in overall statistics of epileptic brains (Spielmeyer, 1927; Scholz, 1951; Sano and Malamud, 1953). Sano and Malamud found Ammon's horn sclerosis in 29 out of 50 anatomically investigated cases. In those cases suitable for such analysis they report a significant correlation between the presence of Ammon's horn sclerosis and the occurrence of clinical and electroencephalographic features of temporal lobe epilepsy during life. From these findings one might have expected a higher incidence of Ammon's horn sclerosis in our material than seven cases out of 12. In all our cases with typical Ammon's horn sclerosis the onset of temporal or generalized epilepsy was below the age of 10 years. Although it is established, of course, that Ammon's horn sclerosis identical in appearance and degree may be produced in epilepsy of onset at a later age it would be of great interest if the frequency of its incidence were higher in infancy and childhood. We are just completing an anatomical analysis of 17 patients who became epileptic after leucotomy (to be published separately), and in only one of these an Ammon's horn sclerosis was found.

The Ammon's horn sclerosis found in temporal lobe epilepsy is in every detail identical with that occurring generally in epileptic brains.

The laminary loss of neurons in the third layer, particularly in the depth of the sulci, together with the typical sclerosis of the Ammon's horn, speaks in favour of anoxia as the causal mechanism in many cases of our second group. Penfield and his collaborators assumed that this anoxia occurred at birth. Against this must be set the widely accepted view elaborated by Spielmeyer and his school, particularly by Scholz (1951, 1953), that Ammon's horn sclerosis in epilepsy results from the functional vascular and anoxic disturbances which accompany (or perhaps precede) severe generalized convulsions. These authors have provided convincing evidence that in some areas the early stages of ischaemic necrosis in the vulnerable sector could not have been produced otherwise than by a preceding severe generalized convulsion. Scholz claims that such convulsions may be particularly deleterious in early infancy and childhood, especially if they occur in connexion with the exanthematous fevers, whooping cough, acute gastric infections, and acute allergic conditions. The damage in the brain thus caused may be considerable, and may reach the proportions of total, lobar, or hemisclerosis and may also affect the cerebellum, thalamus, and other subcortical centres. Most lesions described in our second group would theoretically fit into the Scholz category of post-epileptic damage. Of course, Scholz would not deny that anoxia occurring without convulsions, including, for example, anoxia at birth, may have a similar effect on the brain.

That birth injury is only one possible aetiological factor is well illustrated by a post-mortem observation (outside our operative series). It concerned a boy with no history of birth difficulty who at the age of 8 developed Still's syndrome with swelling of joints, transient rashes, and fever. In the course of this illness a series of generalized convulsions occurred suddenly, lasting for five hours. He remained comatose for three days and developed pneumonia. On recovering from pneumonia he was found to be demented. On several occasions he had recurrences of status epilepticus, but he also had a variety of minor fits including screaming attacks and sudden autonomic disturbances which were thought to point to the temporal lobe. He died 12 months after the first epileptic status. The brain showed widespread damage which will be described in detail in a subsequent paper (Meyer, Beck, and Shepherd). The temporal lobe was severely affected, and, as Fig. 8 demonstrates, showed general cortical atrophy which was particularly marked in the first temporal convolution (and the whole region surrounding the Sylvian fissure) and in the medial convolutions including the Ammon's horn. All the lesions had the characteristics of relatively recent sequelae of anoxia and none of them could histologically have been older than the first status epilepticus. This case thus shows conclusively that the same combination of lesions of the hippocampal region and the first temporal convolution which Penfield and his colleagues ascribed exclusively to a specific mechanism of anoxia and herniation at birth may occur in later life, in this instance, presumably, as a sequel to serial epileptic convulsions at the age of 8 years. It may be mentioned that particular attention was directed in this case to organic disease of the blood vessels but none was found.

The complexity of the aetiological interpretation is reflected in Table II in which some relevant clinical data are plotted against the pathological changes in the 14 cases of our second group. Pathological birth was reported in six cases, but in

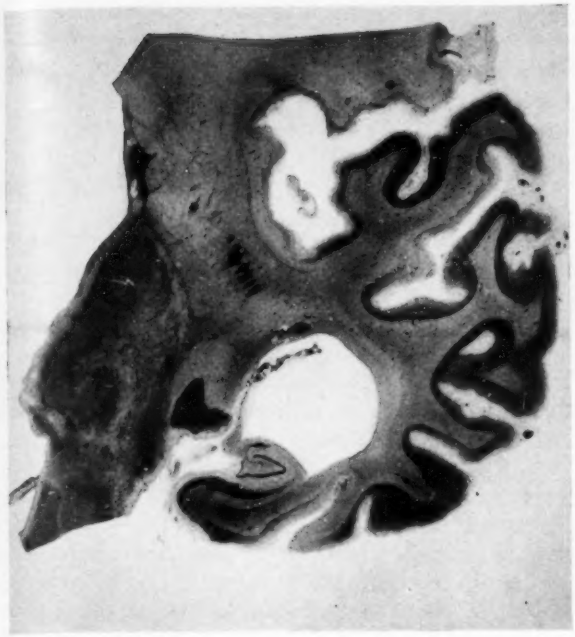


FIG. 8.—Case H. (post-mortem specimen). Atrophy of the tempora lobe and Sylvian region. Within the temporal lobe the atrophy is most marked in the first temporal convolution and the most medial convolutions including the Ammon's horn. The latter shows degeneration of nerve cells within the Sommer sector and end-plate. Nissl stain. × 1·6.

two (Cases 2 and 9) the onset of symptoms was not before the second decade which renders any aetiological connexion tenuous. There is no conspicuous correlation of a history of difficult birth with the major degrees of damage to the Ammon's horn. In Cases 1 and 7, for instance, there was severe Ammon's horn sclerosis without a history of birth injury, while in Cases 9 and 12 with definite birth trauma there were only minor Ammon's horn changes. The onset of epilepsy coincided with childhood fevers in three cases; in one of these (Case 1) an infantile hemiplegia suddenly appeared as a complication of measles, possibly due to a vascular accident (arterial or venous thrombosis) or to an encephalitis; in the other two (Cases 7 and 8) the epilepsy was ushered in by severe serial generalized convulsions. Only in Case 14 was a definite post-natal head injury recorded.

Major convulsive seizures were reported in eight cases and are apparently excluded in three (Cases 4, 11, and 12). In the remaining cases no such seizures were described, but our information covering all phases of each patient is not sufficiently comprehensive to be certain. Only in Cases 7, 8, and 14 is it definitely known that severe generalized convulsions preceded the characteristic temporal lobe attacks.

On the other hand, a typical Ammon's horn sclerosis was found in three cases in which the occurrence of major attacks was, as far as one can tell, either excluded or uncertain. Of these, Case 3 had a history of severe birth injury and subsequently exhibited a congenital type of nystagmus. Case 4 also had a history of severe birth injury, while in Case 8 both birth injury and chickenpox are recorded.

Final conclusions, obviously, must wait until a larger number of cases and more detailed information on the clinical and electrophysiological aspects will be available. We are also inevitably handicapped by not knowing whether similar changes are found in the unoperated temporal lobe or in other parts of the brain. It already emerges, however, from the analysis of the present series that birth injury as a cause of temporal lobe epilepsy in the absence of convulsions is proved or likely in at most only three cases (3, 4, and 12), and that a history of birth injury does not correlate consistently with the presence of Ammon's horn sclerosis. On the other hand, it seems fairly certain that in Cases 1, 7, and 8 events complicating measles, "teething", and chickenpox respectively were responsible for the onset of temporal lobe epilepsy. To these three cases must be added the post-mortem case in which the combination of lesions in the first temporal convolution and Ammon's horn followed a severe status epilepticus during Still's syndrome at the age of 8 years.

It follows then that the aetiological concept of incisural sclerosis caused by tentorial herniation and anoxia at birth put forward by Penfield and his collaborators may have been an over-simplification, and that later events in infancy, childhood, and early adolescence play at least an equal, if not greater, part. This is in agreement with the views expressed by Gastaut (1953) in his recent critical review. Gastaut attached particular importance to trauma and encephalitis, especially measles encephalitis, but in our opinion encephalitis may not be as important as vascular accidents and other anoxic conditions, and, in particular, the anoxia following serial epileptic convulsions during the fevers of childhood, acute gastric infections, and acute allergic conditions of this age period.

However, although their hypothesis requires some modification, the Montreal workers have done a great service by renewing attention upon the Ammon's horn sclerosis whose pathogenic and functional significance still remains an enigma. It is not intended to discuss this complex problem in this paper. Much interesting information on the functions of Ammon's horn has emerged from

TABLE II

CORRELATION OF BIOPSY FINDINGS WITH CLINICAL DATA (EXCLUDING CASES OF TUMOUR) IN 14 CASES OF TEMPORAL LOBE EPILEPSY*

Case, Sex	Age at Onset/ Operation (years)	Clinical Features			Possible Aetiological Factors		Side of Lobectomy	Pathological Features					Results of Temporal Lobectomy	
		Grand Mal Additional to Seizures without Convulsions	Personality Disorder	*X*-ray Findings	Difficult Birth	Other Causes		Meningeal Fibrosis	Marginal Gliosis	Atrophy of Cortex	Gliosis of White Matter	Ammon's Horn Sclerosis	Fits	Personality
1. ES ♀	4/13	+	+	Small L. hemicranium and gross atrophy L. hemisphere	−	Sudden onset of coma and hemiparesis following measles	L	−	++	++	++	++	Free	Improved
2. Man ♀	11/25	+	++	Small L. hemicranium and atrophy L. hemisphere	++	−	L	−	++	++	++	++	Free	Unchanged
3. Pat ♂	3/13	?	++	Small L. hemicranium and hemisphere	++	−	L	−	++	++	+	++	Free	Improved
4. Wa ♂	2/22	−	++	Distorted skull and atrophy right hemisphere	++	−	R	++	++	+	+	++	Much improved	Slightly improved
5. Ch ♂	40/49	+	−	Skull normal. Atrophy L. hemisphere	?	−	L	++	++	−	++	Not available	Free	—
6. Ri ♂	2/32	?	++	? normal	?	−	L	++	++	−	++	Not available	Free	Improved
7. Pr ♂	2/23	+	−	Skull normal. Atrophy R. hemisphere	−	Status epilepticus associated with "teething"	R	+	+	±	−	++	Free	Improved
8. Mac ♂	2/45	?	++	Small R. hemicranium and hemisphere	+	Convulsions at onset complicating chickenpox	R	−	++	±	+	+	Much improved	Unchanged
9. Par ♂	18/25	+	++	Small L. hemicranium and hemisphere	++	Boxer	R	−	++	−	+	±	Slightly improved	Unchanged
10. Ke ♀	4 m./43	+	++	Normal findings	−	−	L	−	+	−	+	+	Died following operation	
11. Le ♂	8/38	−	+	Dilatation temporal horn L. ventricle	−	−	L	−	++	+	+	±	Free	Improved
12. St ♀	2/21	−	++	Small L. hemicranium but cerebral hemispheres equal	+	−	L	−	++	−	−	±	Improved	Improved
13. Lew ♀	30/43	+	+	Normal findings	−	−	L	−	++	±	+	±	Free	Slightly improved
14. Fa ♂	18/45	+	++	Skull normal. Lateral ventricles dilated, left more than right	−	Head injury at 18	R	−	+	±	+	±	Slightly improved	Worse

*Order approximately according to severity of the lesions.

recent experimental physiological research carried out by McLean, Pribram, Kaada, and Delgado, and, from a different angle, by Gastaut and his associates (vide Gastaut, 1953). This structure is now regarded as forming part of the visceral brain or limbic system together with the uncus and amygdaloid nucleus and the so-called transitional cortex of the anterior insula, posterior orbital, and anterior cingular regions. Electro-anatomical investigations have demonstrated the close inter-relationship of these centres and their connexions with the diencephalon. Gastaut and others have shown in experimental animals that behavioural changes similar to those seen in temporal lobe epilepsy can be elicited from these areas by electrical or chemical stimulation. MacLean (1954) believes that the fronto-temporal portion of the visceral brain is specifically concerned with the memories, feelings, and actions related to the oral senses, i.e., to functions which would obviously suggest its major importance to temporal lobe seizures. Other workers relate the visceral brain rather to more general functions. Papez, in his now famous paper, in 1937 regarded a similar combination of centres as a cerebral mechanism for the elaboration of emotion and emotional expression. Herrick (1933), Grünthal (1947), and Le Gros Clark (1950) saw in the Ammon's horn an unspecific activator of cortical function. Our knowledge in this field is still in a state of considerable flux, so that a certain reserve is indicated when basing hypothetical considerations upon it.

The next step in the investigations which our group are undertaking will be to coordinate clinical symptoms, electrocorticographic observations, and the effects of stimulation during the operation with the subsequent anatomical and pathological analysis. The importance of systematic post-mortem studies of clinically and electrophysiologically well-investigated cases of temporal lobe epilepsy must also be stressed. They are bound to give a more comprehensive and clearer picture of the histological changes than the investigation of isolated biopsy specimens, so difficult to interpret, could ever provide.

Summary

The pathological findings in 18 resected temporal lobes of patients suffering from temporal lobe epilepsy and one post-mortem brain have been reported. The surgical cases were all ones in which the pre-operative clinical and radiological studies had failed to demonstrate the presence of space-occupying or other gross circumscribed lesions, but in which electroencephalography had disclosed a unilateral epileptic focus.

The material can be divided into two groups. The first group of four cases contains three small tumours and one case of gross post-traumatic scarring.

The second group of 14 operative and one post-mortem case is much larger and has been especially analysed. All except three of the operated cases were strikingly benefited by the removal of the temporal lobe. Lesions were found in all cases but varied considerably in quality and degree. In many cases a laminary atrophy, particularly of the third cortical layer, often situated in the depth of the sulci, was found and interpreted as a consequence of anoxia. Ammon's horn sclerosis was found in seven of 12 cases, interestingly in all cases with onset of the disease before the age of 10. It was correlated neither with a history of birth injury nor with that of preceding major convulsions. Birth injury as the cause of the epilepsy was proved or likely in at most three cases. On the other hand, three cases of temporal lobe epilepsy followed a cerebral complication (probably vascular accident or encephalitis) during measles, status epilepticus following " teething", and chicken-pox respectively. To these must be added a post-mortem case in which lesions with characteristic distribution followed status epilepticus in the course of Still's syndrome at the age of 8 years.

It was concluded from this preliminary investigation that incisural sclerosis resulting from birth mechanisms cannot be maintained as an exclusive aetiology and that later events in infancy, childhood, and early adolescence play at least an equal part.

Our thanks are due to Dr. Denis Hill and Dr. D. A. Pond for investigating and referring for operation most of the patients studied in this series, to Dr. R. Hoare for the radiological examinations, and to Dr. W. Mitchell and Dr. G. Pampiglione for some of the clinical data. We are also indebted to Miss Edna Walker for her technical help and to the Bethlem Royal and Maudsley Hospital (Research Fund) for an expenses grant. Much of the information collected in this paper was communicated by one of us (A. M.) to the Association of British Neurologists at their spring meeting on April 23.

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THE RETICULAR PERIVASCULAR TISSUE OF THE CENTRAL NERVOUS SYSTEM

BY

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Since changes occurring in the nerve cell body and its processes in consequence of trauma or disease produce effects which must obviously be of fundamental importance to the functioning of the nervous system as a whole, the central position in the field of neuropathological research has naturally for many years been occupied by the neuron. The focusing of attention on the neuron has had, however, the unfortunate effect of producing a consequential disregard of other elements. The neglect to which the neuroglial elements of the nervous system were for a long time subject was remedied, at least to some extent, when adequate staining methods were developed for the demonstration of these structures. The evolution of gold and silver impregnation methods enabled great advances to be made in the understanding of the role played by the neuroglia in normal and pathological processes. At the present time, although it is well recognized that perivascular accumulation of cells are a feature of such diseases as encephalitis and poliomyelitis, the relationship of such exudates to the blood vessel and its sheath on the one hand, and to the nervous tissue proper on the other, has been subject to considerable confusion and much misinterpretation. It is the purpose of this paper to suggest that the application of a suitable staining method can lead to the better understanding of the extent and intimate associations of the reticular perivascular sheath, its relationships to the meninges, to the true and artefact perivascular spaces, and thus of its reaction to and implication in disease processes.

The first investigators to recognize that the blood vessels entering the central nervous system were accompanied by reticular perivascular sheaths derived from the lepto-meninges were Key and Retzius (1876) who described the sheaths as formed by visceral and parietal layers continuous with the linings of the subarachnoid space. They injected gelatine coloured with Berlin blue into the subarachnoid space of human cadavers and, as a result of their experiments, were in no doubt that the space between the two layers of this reticular lepto-meningeal sheath was freely in communication with the general subarachnoid space. Earlier workers (Virchow, 1851 ; Robin, 1859 ; His, 1865), and indeed some later ones also (Bevan Lewis, 1889 ; Bruce and Dawson, 1911) appear to have been preoccupied with the search for the lymphatics of the brain. Most of these workers failed to appreciate that the tissue surrounding the blood vessels was lepto-meningeal in origin and regarded this sheath simply as the tunica adventitia of the vessel. They believed that the perivascular spaces were lymphatics related to the tunica adventitia of the blood vessels entering the central nervous system. There was, however, no general agreement as to the exact situation of these spaces. Even Virchow (1851) and Robin (1859), whose names are conjoined in the eponymous nomenclature of the perivascular space, did not agree in their descriptions of its situation: Virchow regarded the spaces as " sub-adventitial " and open to the subarachnoid space, while Robin believed them to be closed and " intra-adventitial " spaces. Cushing (1926) indeed remarked in his *Studies in Intracranial Physiology and Surgery* that " these distinguished investigators originally gave such casual descriptions of the spaces in question that it is surprising that they should have become eponymic." Tuke (1894) recognized the meningeal origin of the perivascular sheaths but regarded the perivascular space as lymphatic in nature and as responsible for the removal of waste and superfluous material ; indeed he went so far as to suggest that the perivascular space was the beginning of a lymph path which ultimately ended in the lymph glands of the head and neck.

Most of these workers based their descriptions of the perivascular sheaths upon the examination of pathological material and were handicapped by the inadequate histological techniques available to them. Furthermore, with the notable exception of His

(1865), they seldom attempted to supplement their descriptions by the employment of experimental procedures involving the use of indicator substances. His used a multiple intracerebral puncture technique and was able to inject spaces around the blood vessels within the nervous system. He recognized that these spaces were not the true perivascular, or Virchow-Robin, spaces, and, since in his opinion they were bounded by cells of an endothelial type and communicated with subarachnoid "lakes" situated between the brain tissue and the surface pia mater (epispinal spaces of His), he termed them "lymphatics". Unfortunately the clear distinction drawn by His between the spaces he injected and the Virchow-Robin spaces was soon lost sight of and subsequent workers appear to have regarded them as identical. Thus, far from clarifying the picture of the reticular sheath and perivascular space around the blood vessels, the researches of His increased rather than diminished the confusion surrounding their description.

The absence of agreement as to the anatomy of the lepto-meninges renders more difficult a clear understanding of the nature, identity, and connexions of the reticular perivascular sheath. By some authorities stress is laid on the separate identity of the pia mater and the arachnoid mater and, in consequence, the exact identification of the layers forming the perivascular sheath becomes a question of some importance. Tuke (1894) regarded the vessels as carrying prolongations of the pia mater with them into the brain substance. He thought that this pial sheath replaced the adventitial layer of the blood vessels within the central nervous system, and that it surrounded the blood vascular system to its ultimate branches. Mott (1910) held views on the nature of the perivascular sheath very similar to those of Tuke. He was the first to consider that there were differences in the nature and extent of the sheaths between the arteries and veins. Mott thought that the perivascular sheaths were better marked around the arteries than around the veins: he also noted that the sheath was continued over the capillaries. Hughson (1925) believed that the outer wall of the perivascular sheath was formed by the turning inwards of the pia mater, whilst the layer on the vessel itself, forming the inner layer of the sheath, was derived from the cells of the arachnoid mater. Schaltenbrand and Bailey (1928) in their descriptions referred to the "pia-arachnoid", apparently regarding the lepto-meninges as forming a single entity. They did not concern themselves greatly with the subdivision of the perivascular sheath into pial and arachnoid components and were content to regard the sheath as formed by a sheet of reticular connective tissue equivalent to the pia-arachnoid. At the same time the pial nature of the outer layer of the sheath was implicit in their description of this layer as a "piaglialmembran". One of the most recent accounts of the reticular perivascular sheaths was that given by Patek (1944). He reaffirmed the description of Key and Retzius (1876) and regarded the arachnoid mater as forming the inner layer of the perivascular sheath, but differed from them in regarding the pia mater as providing only the peripheral part of the outer layer of the sheath. In his view the deeper parts of the outer layer had the form of a fenestrated membrane: this standpoint will be considered later.

A consideration of the findings outlined above suggested that an experimental technique which combined the use of an indicator substance with a staining method specific for reticular tissue appeared likely to throw new light on the nature and extent of the reticular perivascular sheath, and its relationship to the perivascular spaces.

Material and Methods

Histological examinations were carried out on 40 albino rats and on human material from the central nervous systems of a full-term foetus and of patients who had died following epidemic encephalitis and anterior poliomyelitis.

Newborn albino rats were used for experimental observations employing an indicator substance introduced into the cranial subarachnoid space. Briefly this method consisted in the daily injection, from birth and continuing over a period of about three weeks, of a small amount (0·05 to 0·1 ml.) of colloidal carbon into the cranial subarachnoid space. The injection caused only a very temporary disturbance from which the animal recovered in a few minutes. The alteration in intracranial pressure produced by the quantity of the indicator employed was evidently quite compatible with life, and might therefore be regarded as within the limits of normal physiological pressures. At the end of three weeks the animals were sacrificed. The brains and spinal cords were removed carefully, keeping the lepto-meninges intact as far as possible, and subjected to the same histological examination as the human material.

The tissues were fixed, embedded in paraffin, and sectioned in the usual manner. A variety of stains was employed, including haematoxylin and eosin, toluidine blue, Mallory's trichrome stain, and a modification of Bielschowsky's stain. It was found that the application to the central nervous system of a modification of the stain for reticular and collagenous fibrils described by Long (1948) yielded the most valuable information. This method gave excellent results with formalin-fixed material.

The details of the method are as follows. The sections are dewaxed and carried through descending grades of alcohol to distilled water. Then they are treated with

0·25% aqueous solution of potassium permanganate for five minutes, washed in running water for five minutes, and rinsed in distilled water. They are placed in 5% oxalic acid for five minutes and then washed in running water for five minutes. They are washed in three changes of distilled water for 10 minutes. The sections are placed in a 5% solution of silver nitrate for 12 hours in the dark, washed in four changes of distilled water, and treated with ammoniacal silver carbonate in an oven at 40 to 45°C. for 30 minutes. The ammoniacal silver carbonate is prepared as described by Long but diluted to a 25% solution by the addition of double glass-distilled water. When the sections are removed from this solution they should be golden brown. Each slide is dipped separately in a jar containing four drops of ammonia in 500 ml. distilled water and then transferred to 1% neutral formalin for 10 minutes. The sections are washed in running water for 10 minutes and then rinsed in distilled water. The sections are toned in 0·005% gold chloride for 15 minutes, washed in distilled water, and fixed for five minutes in 5% hypo., and washed in running water. The sections are stained with 1% neutral red for 10 minutes at room temperature and differentiated in 70% alcohol. They are dehydrated, cleared, and mounted in neutral balsam. The reticular perivascular sheath and lepto-meninges are stained a purplish-black, the neurons red, and the background pink.

The use of this modification of Long's stain makes it possible to stain quite specifically the reticular perivascular tissue and to identify with considerable certainty its relationship to other structures.

Results

Normal Material.—The description which follows of the arrangement of the reticular tissue related to the blood vessels of the central nervous system is derived equally from the examination of the nervous system of the experimental rats and from the human full-term foetal material except where indicated. There do not appear to be any significant differences between man and the rat in regard to this reticular tissue, nor would one expect to find such differences. The account is a general one based upon the examination of a large number of sections from many animals and individual specimens will not be described.

Each blood vessel carries with it into the central nervous system a reticular sheath which is continuous with the lepto-meninges and is clearly derived from them (Fig. 1). Except over the larger segmental branches this reticular tissue is small in amount and appears as a thin layer immediately external to the muscle cells of the tunica media. It may be noted here that, within the central nervous system, no distinct adventitial layer can unequivocally be recognized in the walls of the blood vessels. The reticular sheath extends over the arteries, the arterioles, the larger capillaries, the venules, and the segmental veins. In addition, it is not possible to be certain whether a very thin layer may not also separate even the smaller capillaries from the nervous tissue proper.

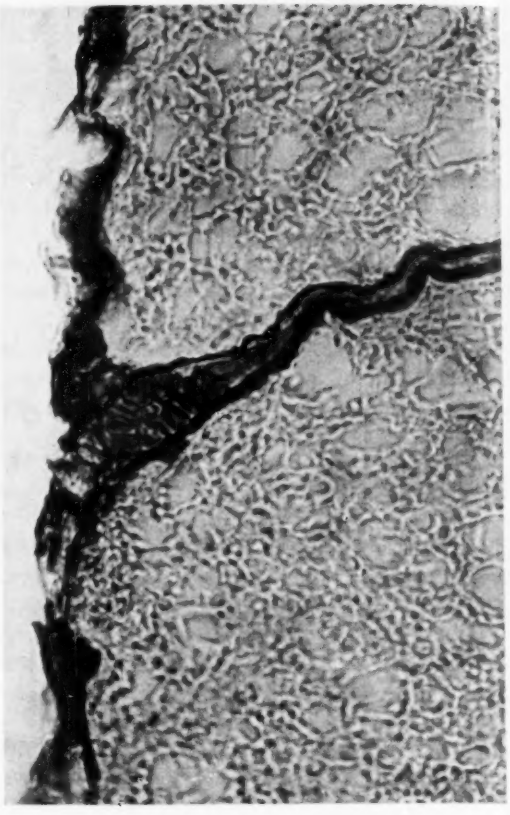

FIG. 1.—Transverse section through the spinal cord of a young rat. The section shows a blood vessel entering the cord, and demonstrates the continuity of the pia-arachnoid with the reticular perivascular sheath. Stained by a modification of Long's stain. × 760.

In normal material the two-layered nature of the reticular perivascular sheath is only apparent in relation to the larger segmental vessels. The smaller vessels present no evident separation of the reticular sheath into two layers, although the examination of pathological material suggests that such a separation can be made to appear by the splitting of the reticular sheath.

In many specimens, particularly when intravenous hypertonic saline has been administered to the animal before death, the blood vessels are separated from the nervous tissue itself by spaces of divers dimensions. The outer walls of these spaces show no lining membrane, but their inner walls are formed by the external surface of the reticular sheath, and are separated from the vessels by the whole thickness

FIG. 2.—Transverse section through the spinal cord of a full-term human foetus. The reticular sheath of the blood vessel is separated from the nervous tissue by an empty trabeculated space, the artefact perivascular space. Stained by a modification of Long's stain. × 800.

of the perivascular tissue (Fig. 2). These spaces can often be followed to the surface of the spinal cord where their continuity with the epispinal space of His is unequivocal. There can be no doubt that these spaces are in fact the artefact perivascular spaces and not the true perivascular spaces of Virchow-Robin.

The subarachnoid injection during life of an indicator such as colloidal carbon makes possible the identification of the perivascular spaces in histological preparations by the observation of small particles of carbon lodged alongside the blood vessels in the depths of the nervous tissue. In favourable sections, when the lepto-meninges have been carefully preserved, it is possible to demonstrate with certainty the continuity of this carbon with that lying in the general subarachnoid space (Fig. 3). These perivascular carbon particles are lying between the two layers of the reticular perivascular sheath and are separated from the artefact perivascular space by the outer layer of this reticular tissue. It follows that the true perivascular space of Virchow-Robin, which opens freely exteriorly into the subarachnoid space, lies between the two layers of the reticular perivascular sheath.

One of the most striking conclusions that is compelled from the examination of sections of the central nervous system of rats which have received colloidal carbon during life is the relative paucity of the perivascular spaces. Generally only the larger vessels entering or leaving the nervous tissue show perivascular carbon particles. These vessels are few, sometimes only one or two in 0·1 mm. of the spinal cord. It follows that, although potential spaces may exist, only a small number of true perivascular spaces can, in fact, be observed in normal nervous tissue.

Pathological Material.—The pathological material examined comprised sections from the brains and spinal cords of patients who had died following attacks of anterior poliomyelitis or epidemic encephalitis. Since only the part played by the reticular perivascular sheaths in the disease processes was of interest in this investigation no particular

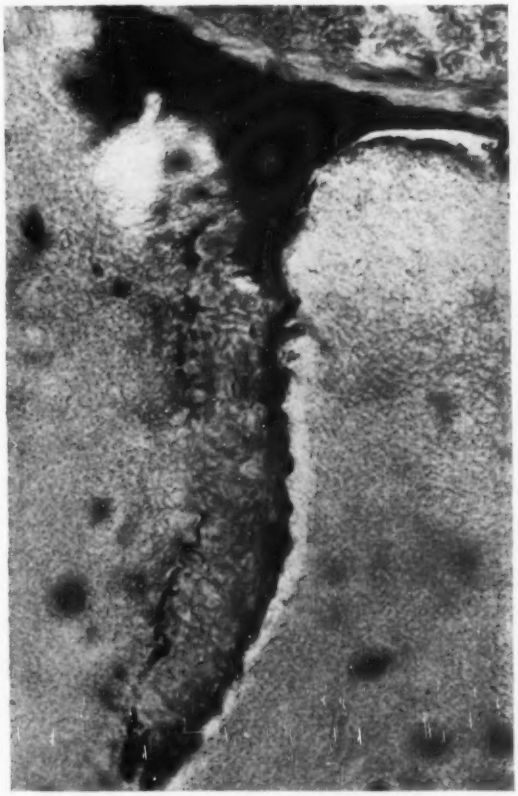

FIG. 3.—Section through the cerebral hemisphere of a young rat which had received a daily subarachnoid injection of colloidal carbon from birth until the age of 21 days when it was killed. The continuity of the carbon in the true perivascular space with that in the subarachnoid space is shown. The clear space separating the colloidal carbon from the brain tissue is the artefact perivascular space. Stained by haematoxylin and eosin. × 625.

attention was paid to the details of neuronal destruction or reaction.

In sections from the diseased brains and spinal cords the blood vessels appeared more conspicuous than in sections from normal material. This prominence may have been due largely to the well marked perivascular exudates which formed cuffs around the blood vessels. In sections stained by toluidine blue or by Mallory's trichrome stain the perivascular collections of cells can be clearly recognized (Figs. 4 and 5), but it is impossible to determine exactly their relationship to the reticular perivascular sheath. From the examination of these sections one cannot state unequivocally whether the cells are lying within the true perivascular space or in the artefact perivascular space, nor, indeed, whether they might not be lying within the adventitia (if this exists) of the blood vessel itself. On the other hand in sections which have been treated by the modification of Long's method the reticular perivascular sheath is readily distinguished (Fig. 6). In these latter sections it can be seen that the perivascular collections of inflammatory cells are, at least for the most part, contained within the Virchow-Robin spaces. They are separated from the wall of the blood vessel by the inner layer of the reticular tissue and from the neurons by the outer lamina of the reticular sheath. Outside the reticular perivascular sheath can sometimes be seen a space, the artefact perivascular space, which is relatively free from cells (Fig. 7). Even quite small vessels show this perivascular cuffing and the separation of the reticular tissue into an inner and an outer layer, which in sections of normal tissue may not be seen, is now quite evident. The true perivascular spaces are closely packed with cells. It would appear that under pathological conditions the perivascular spaces are more extensive than in normal tissue. Whether this is due to the opening up of already existing potential spaces, which are not evident under normal conditions, or by the extension inwards of the perivascular spaces around the larger vessels splitting the reticular tissue into two layers, is difficult to determine. It would however seem unlikely that the latter process could occur to any marked extent.

In some of the sections stained with the modified Long's stain the outer lamina of perivascular reticular tissue shows a somewhat rough and shaggy appearance, in contrast to the sharply delineated appearance which it normally presents. The reticular

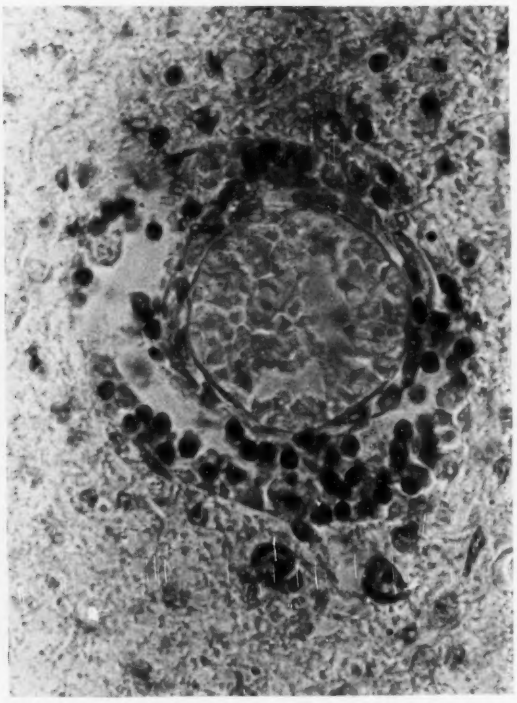

FIG. 4.—Transverse section through the spinal cord of a patient who died of poliomyelitis. The cellular exudate can be seen around the blood vessel (compare with Fig. 6). Stained with toluidine blue. × 500.

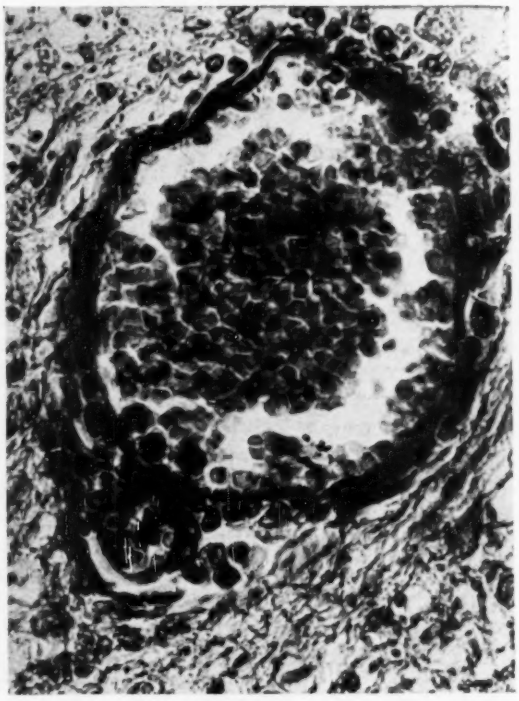

FIG. 5.—Transverse section through the same spinal cord as is shown in Fig. 4. The position of the cellular exudate in relation to the blood vessel is shown (compare with Fig. 6). Stained with Mallory's trichrome stain. × 500.

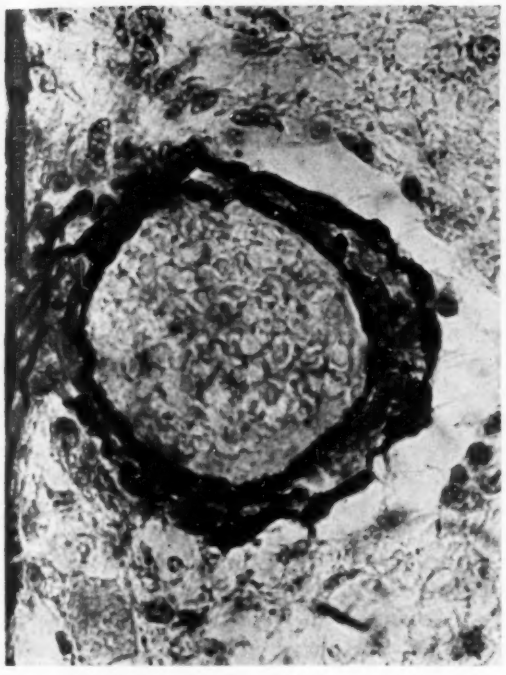

FIG. 6.—Transverse section through the same spinal cord as is shown in Fig. 4. The cellular exudate can clearly be seen to be confined to the space between the two layers of the reticular perivascular sheath, i.e., the true perivascular space. External to the outer layer of the sheath can be seen the artefact perivascular space. Stained by a modification of Long's stain. × 625.

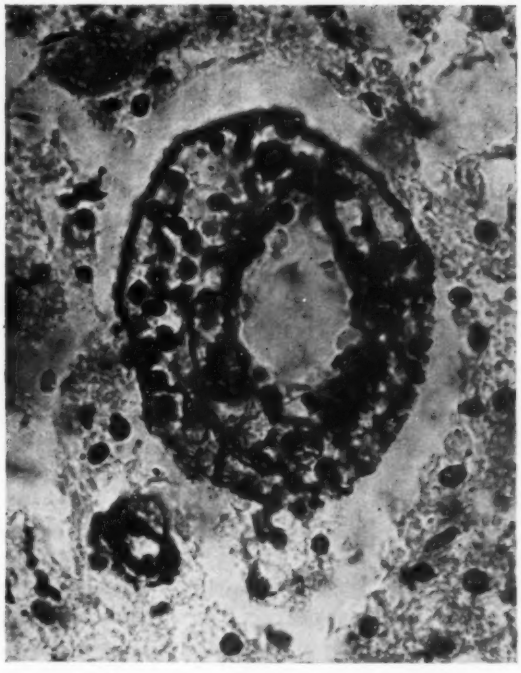

FIG. 7.—Transverse section through the spinal cord of a patient who died from encephalitis. The cellular exudate is seen to lie in the true perivascular space. External to the outer layer of the reticular perivascular sheath lies the artefact perivascular space, which contains only a few inflammatory cells. Stained by a modification of Long's stain. × 625.

tissue appears to be sending processes into the surrounding nervous tissue (Fig. 8). Such an appearance is highly suggestive of the occurrence of a proliferative reaction of the reticular tissue, although the material available for examination was insufficient to enable a definite decision to be reached on this point.

FIG. 8.—Transverse section through the spinal cord of a patient who died from poliomyelitis. The proliferation into the surrounding nervous parenchyma of the reticular perivascular sheath of a small blood vessel may be seen. Stained by a modification of Long's stain. × 1820.

Discussion

Many of the misconceptions as to the nature, extent, and functions of the Virchow-Robin spaces have arisen from the failure to employ techniques which enabled the clear differentiation of the reticular perivascular sheaths to be made, and the recognition that this reticular tissue formed the inner and outer walls of the true perivascular spaces.

Before the evolution of silver and gold impregnation techniques workers were handicapped by their inability to distinguish clearly between the nervous and non-nervous elements of the central nervous system. It was, almost certainly, the absence of adequate staining methods that was responsible for the description by many of the earlier workers of the

reticular perivascular sheath as the adventitia of the cerebral blood vessel (Virchow, 1851 ; Robin, 1859 ; His, 1865 ; Obersteiner, 1890 ; Bevan Lewis, 1889). There is little doubt that, for the most part, their accounts refer to the reticular perivascular sheath. Nevertheless the absence of an adequate staining method was almost certainly responsible for some unfortunate misconceptions that, up to the present day, have influenced views as to the functions of the perivascular spaces.

It is against this background that the classical work of Key and Retzius (1876) stands out as a landmark in the history of the reticular perivascular sheaths. They recognized that the blood vessels entering the brain were accompanied by endothelial-lined perivascular spaces, and were the first to differentiate the reticular sheath into an outer layer derived from the pia mater and an inner derived from the arachnoid. They distinguished between the true perivascular space (of Virchow-Robin) and the artefact space described by His. In their account, however, they stated that the true perivascular space was intra-adventitial in position. It is evident that their use of the term adventitial was different from that commonly accepted to-day. It is unfortunate that this different usage of the term has contributed to the subsequent misinterpretation of their work.

Tuke (1894), while recognizing that the perivascular sheaths were derived from the leptomeninges and replaced the adventitial layer of the blood vessels within the central nervous system, believed that these sheaths surrounded the blood vessels to their ultimate branches and gave off processes which provided each neuron with a perineuronal capsule. At this distance in time it is impossible to say whether he was influenced in this belief by his conception of the perivascular system as responsible for the removal of waste and superfluous material from the nerve cells. The views of Mott (1910) have strongly influenced the beliefs of subsequent workers in this field : Cushing (1926), for example, was so impressed by Mott's work that he considered " no better description of the spaces existed in the English language ". Mott's interest, like that of Tuke, arose primarily from his examinations of the brain in cases of insanity. Although Mott carried out some experimental work, his research was hampered by the absence of a suitable staining method for the reticular tissue and his failure to employ an indicator substance. His view as to the position of the perivascular space between the prolongations of the lepto-meninges is the generally accepted one but in his interpretation of sections of nervous tissue he wrongly identifies this space with the artefact space lying outside the reticular sheath. This error led him to expound the view that the perivascular spaces were part of a complex perivascular system continuous on the one hand with the perineuronal spaces and on the other with the subarachnoid space. A comparison of Mott's illustrations with sections stained to show the reticular tissue leaves no doubt that the spaces described by him as the true perivascular spaces are in fact the spaces observed by His (1865) who recognized them to be artefacts.

Although Weed (1914) did not employ histological techniques which would allow him to contribute to the better understanding of the reticular perivascular sheaths his contribution to the field of research into the circulation of the cerebrospinal fluid is such that his views cannot be ignored. Weed appears to have accepted without question the views expressed by Mott on the communication between the perineuronal and the perivascular spaces, thereby implying that there was no barrier interposed between the perivascular spaces and the nervous tissue by the outer layer of the reticular sheath. The experimental work of Weed, using the Prussian blue technique, was designed to answer problems concerned with the circulation in these channels of the cerebrospinal fluid and was not such as to enable him to verify or disprove the assumption upon which his work depended. The defects of the Prussian blue technique have been pointed out by Patek (1944) and their analysis is outside the scope of this article. It suffices to say that Weed's experiments did not throw any new light on the nature and arrangement of the reticular perivascular sheath.

Of more recent accounts the only ones that appear worthy of detailed consideration are those of Schaltenbrand and Bailey (1928) and Patek (1944). Schaltenbrand and Bailey (1928) based their descriptions essentially on the examination of pathological material. They were in agreement with Key and Retzius in recognizing the leptomeningeal nature of the perivascular sheaths. In one respect, however, they disagreed with earlier writers : they regarded the outer layer of the sheath as formed not only by the pia mater but also by the glia fused with it to form a " piaglialmembrane ". On this concept of a " piaglialmembrane " was based their postulation of the to-and-fro movement of this membrane under certain conditions, thereby increasing or diminishing the size of the Virchow-Robin space at the expense of the artefact space. It may be noted that this view of the functioning of the perivascular spaces has not received the support of other workers in this field. Schaltenbrand and Bailey also considered that even the smallest capillaries

were covered by a reticular perivascular sheath and surrounded by a Virchow-Robin space. Woollard (1924) was, however, of the opinion that the cell nuclei in relation to the capillaries, upon the presence of which they appear to have based their view, were neuroglial in origin. It is only fair to state that in a recent paper Schaltenbrand (1953) remarked that the perivascular spaces exist only round the larger vessels of the brain and that round the capillaries there is only a little connective tissue. If one ignores the thesis of a "piaglialmembrane" the views of Schaltenbrand and Bailey on the reticular perivascular sheaths accord very closely with those expressed earlier by Key and Retzius (1876).

The work of Patek (1944) on the reticular sheaths and the perivascular spaces does not appear to have received the recognition which it merited. Patek employed colloidal mercuric sulphide as an indicator and combined its use with that of intravenous hypertonic saline. From his experiments and subsequent histological examinations he concluded that the inner layer of the reticular perivascular sheath was derived from the arachnoid mater. He considered that this layer accompanied the arteries and veins as far as the arterioles and venules as a complete membrane. Patek was unable to recognize a continuous covering over the capillaries. His view of the outer layer of the perivascular sheath was unique in that he regarded the pia mater as extending along the arteries for only a very short distance and being then replaced by a fenestrated membrane. On the veins the pia mater extended as far as the venules and then terminated in the same manner. In the opinion of Patek the outer wall of the perivascular space was formed, in its deeper part, by a glial membrane. Patek's work implies that the inner and outer walls of the reticular sheaths do not fuse at the inner ends of the perivascular spaces and indeed he describes the fluid in the perivascular spaces as becoming continuous with the tissue fluid of the brain. The views of Patek with regard to the termination of the outer wall of the perivascular space are not borne out by the present investigation. In sections stained by the modified Long's method it can be seen clearly that the outer wall of the perivascular space formed by reticular tissue continuous with the pia mater on the surface of the nervous system extends much deeper into the nervous tissue than he suggests. Furthermore, if the reticular sheaths are open at their inner ends it is difficult to see the mechanism by which the flask-shaped distension of the perivascular spaces is produced in torula meningitis (Schaltenbrand and Bailey, 1928).

When one considers the confusion that exists concerning the normal histology of the reticular perivascular tissue it is not perhaps surprising to find that the relationship of these reticular perivascular sheaths to pathological processes is subject to the same confusions and misconceptions. Even in standard textbooks (Boyd, 1950) one finds the Virchow-Robin spaces described as adventitial spaces whilst the artefact perivascular spaces (of His) are regarded as the perivascular spaces proper. The use of a suitable reticular stain makes it possible to identify clearly the inner and outer layers of the reticular sheath, and to recognize that the inflammatory cells around the vessels are essentially confined to the true perivascular spaces (of Virchow-Robin) bounded by these layers. The perivascular spaces often appear to be completely filled, and perhaps even distended, by densely packed inflammatory cells. This finding, together with the observation that in some instances the reticular tissue appears to be undergoing a proliferative reaction, suggests that the reticular perivascular sheaths may play a less passive role in the processes of disease than is generally attributed to them.

Summary

The clear identification of the reticular perivascular tissue of the central nervous system is important to the better understanding of the relationships between this tissue and the blood vessels on the one hand and the nervous tissue on the other.

Much of the confusion in the literature concerning the reticular perivascular tissue derived from the failure of investigators to employ suitable histological techniques for its definition. In consequence the artefact perivascular space has often been identified wrongly with the true perivascular (Virchow-Robin) space.

A modification of Long's (1948) stain for reticular and collagenous fibrils was applied to the study of material from the central nervous systems of laboratory rats. These rats had received daily subarachnoid injections of colloidal carbon for a period of three weeks from birth before being sacrificed. Sections from the brains and spinal cords of patients who had died following attacks of poliomyelitis and epidemic encephalitis were also stained by this method.

The examination of the normal material confirmed the continuity of the outer layer of the reticular perivascular sheath with the pia mater and of the inner layer with the arachnoid mater. It was found that the reticular tissue surrounded all the blood vessels within the substance of the central nervous system with the possible exception of the smaller capillaries.

The reticular stain rendered easy the recognition and delimitation of the perivascular (Virchow-

Robin) spaces and made it possible to distinguish unequivocally these spaces from the artefact perivascular spaces.

The application of the reticular stain to pathological material enabled the position of perivascular exudates within the true perivascular spaces to be clearly recognized. The examination of the sections revealed also a shaggy appearance of the reticular perivascular tissue which suggested that this tissue might perhaps be undergoing a proliferative reaction in response to the processes of disease.

We wish to thank Professor J. D. Boyd for his advice and encouragement. Our thanks are also due to Professor Dorothy Russell and Dr. A. M. Barrett for the supply of material, to Mr. T. R. L. Brooks for photography, and to Mr. R. Smith for technical assistance.

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CASE REPORT: PRENATAL OCCLUSION OF THE INTERNAL CAROTID ARTERY

BY

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The following case is reported as a contribution to our knowledge of the aetiology of "congenital" hemiplegia.

Case Report

A baby girl, I. (NP. No. 363/53, A. 168/53), died about one and a half hours after her birth on May 13, 1953. The pathological findings were those of erythroblastosis foetalis.

She was the fourth child of an Rh-negative mother and an Rh-positive and homozygous father. The first child was born at full term. The second was stillborn at full term. The mother was given A.C.T.H. before the birth of her third infant, who was born alive at full term but required a replacement transfusion and had a positive Coombs test.

For five weeks before the premature delivery of this fourth infant the mother had received 100 mg. of cortisone daily. The pregnancy was normal and there was no antenatal haemorrhage to suggest premature separation of the placenta. Her albumin antibody titre was 1·64. The infant was born by mid-forceps delivery. The very large, oedematous placenta was manually expressed. The obstetrician considered it otherwise grossly normal.

Necropsy

Necropsy was performed three hours after death. The infant was immature, weighing only 2,250 g., in spite of severe generalized oedema of subcutaneous and muscular tissues and large effusions in the serous cavities. There was also oedema of the larynx. The placenta was very much enlarged by oedema and weighed 945 g., whereas the weight of the normal placenta is considered to be one-seventh the weight of the infant, which would be about 320 g. in this case. No further gross pathological lesions were found in the placenta to account for its enlargement.

The large spleen weighed 45 g. and contained a small infarct. The liver was also enlarged. The hypertrophied heart weighed 31 g. and its cavities were dilated, possibly due to increased blood volume. The foramen ovale was widely patent and there was a small patent ductus arteriosus. The lungs were atelectatic. The thymus was hypoplastic, weighing only 1 g.

Microscopical examination showed hyperplasia of the bone marrow, with marked proliferation of cells of the erythroblastic series. The liver, kidneys, adrenals, and spleen showed extramedullary haematopoiesis. There were enormous numbers of erythroblasts and a diminution in formation of lymphocytes. The latter finding was considered to account for the hypoplasia of the thymus. The presence of a small infarct in the spleen was confirmed microscopically, but an arterial embolic occlusion could not be demonstrated even by interrupted serial microscopic sections.

A detailed histological examination of the placenta confirmed oedema of the villi. The capillaries contained numerous erythroblasts. A few small areas of infarction, with necrosis of placental villi, were found, a possible site of origin of an embolism of the foetal circulation.

Examination of the Head.—The scalp tissues were oedematous and haemorrhagic. There was subperiosteal and slight extradural haemorrhage in relation to the bones of the cranial vault. There was no subdural haemorrhage and the tentorium cerebelli was grossly normal.

Brain.—This was examined after fixation in 10% formol-saline for 48 hours. The organ showed prematurity, weighing only 215 g. but the convolutions (Fig. 1) were moderately well formed throughout. There was palpable softening of the cortical distribution of the left middle cerebral artery (Fig. 1), and a horizontal section through the cerebral hemispheres (Fig. 2) confirmed early softening in the complete distribution of this vessel. A dissection of the left internal carotid and middle cerebral arteries showed the lumen of the internal carotid to be occluded by well-defined, white, solid material. This occluding tissue extended to the termination of the internal carotid and for a short distance into its posterior communicating, anterior and middle cerebral branches. The extent of the occlusion was determined by limited serial histological sections and satisfactorily accounted for the softening in the distribution of the left middle cerebral branch. The white colour and the sharp limitation of the occluding tissue were much more suggestive of embolus than of thrombus forming *in situ* on the vessel wall, as the softening in the middle cerebral distribution was estimated as being of only a few days' duration.

The material occluding the lumina of these vessels does not have the histological characters either of a thrombus formed *in situ* or of a blood embolus from a distant

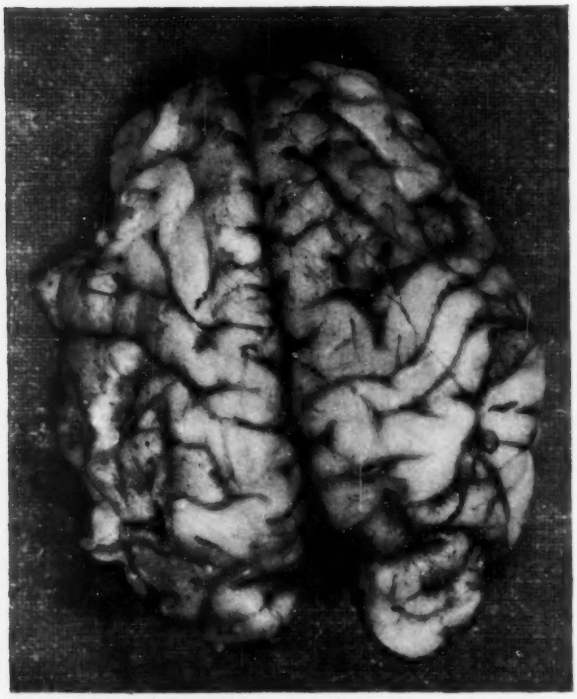

FIG. 1.—Cerebral hemispheres seen from above, showing early cortical softening with a few petechial haemorrhages in the distribution of the left middle cerebral artery.

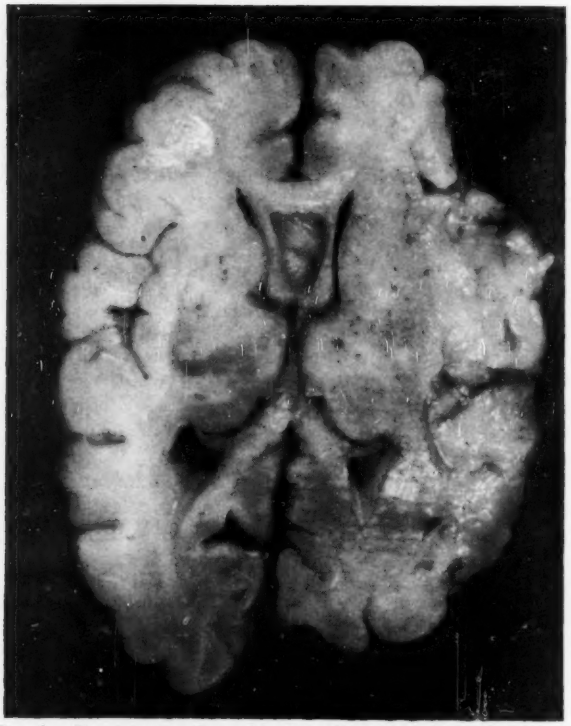

FIG. 2.—Upper cut surface of horizontal section of cerebral hemispheres. This shows softening of a few days' duration in the complete distribution of the left middle cerebral artery (to the right of the photograph). There is a large fifth ventricle.

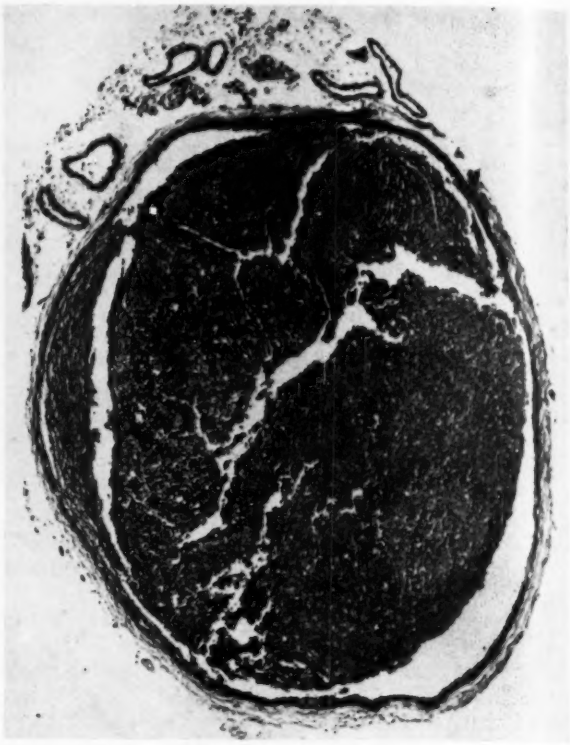

FIG. 3.—Transverse section of the left internal carotid artery at its bifurcation. The lumen of the vessel is occluded by embolic material, the exact origin of which could not be determined.

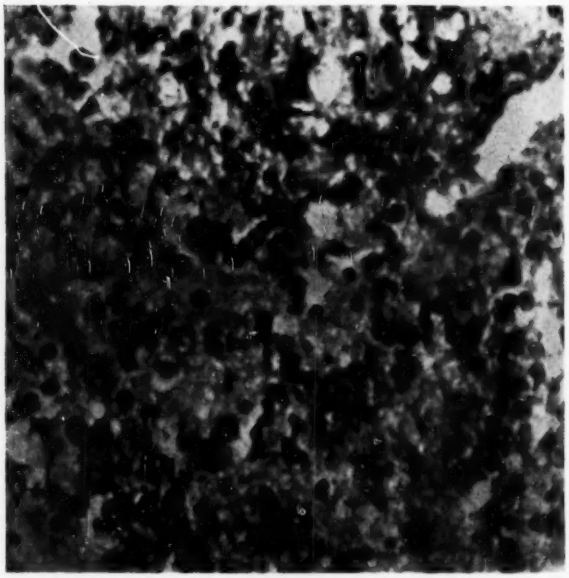

FIG. 4.—Medium-power photomicrograph of the embolic tissue (Fig. 3). It appears to be composed of "dead" cells with degenerating hyperchromatic nuclei. Some of the nuclei are those of erythroblasts from the circulating blood. This occluding material may be dead tissue from the infant's severely diseased placenta.

focus (Figs. 3 and 4). The main mass of the material appears to be dead tissue, the origin of which cannot be determined. It is infiltrated with moderate numbers of red blood corpuscles, many of which contain nuclei. The vessel wall shows early reactive inflammatory changes, maximum in amount at the point of adhesion of the occluding material to the intima (at bottom of Fig. 3). This suggests the possibility of thrombus formation *in situ* but such changes could be produced by the pressure of an embolus. The extent of the reaction indicates that the occlusion had been present for at least some days.

The softened cortex and white matter in the left middle cerebral distribution shows the severe vacuolation of early softening. Fully formed lipoid-filled histiocytes are seen in the cortical tissue and white matter, and there are similar microglial cells, filled with lipoid, in the subarachnoid space overlying the softened cortex. Sections stained with Scharlach R confirm early phagocytosis of fatty degenerative products by microglial cells in the white matter. This would date the softening as being of three days to one week of age.

It seems likely, therefore, that the middle cerebral occlusion occurred, in this case, during the last few days of pregnancy. Embolism appears more probable than thrombosis *in situ*, and, in the absence of another source, an embolus of infarcted, necrotic placental tissue is suggested.

The infarct found in the spleen was probably also due to arterial embolic occlusion, although an occluded artery could not be found even after detailed microscopical examination.

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CASE REPORT: HAIRY TERATOMATOUS CYST IN THE OCCIPITO-CEREBELLAR REGION*

BY

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Teratomas are extremely rare intracranial lesions and their frequency in the neurosurgical series of brain tumours is very low, only about 0·2% in the material of Harvey Cushing (1932), and in the large experience of Dandy (1945) no examples were recorded. Logue and Till (1952) reported seven cases and reviewed the literature, stressing the frequency of intracranial infection as a complication of this kind of tumour. The presence of hair within the cyst of the teratomas has been considered very uncommon and it is also very rare in those series of infants where the incidence of these tumours is higher (Ingraham and Bailey, 1946).

In our experience of more than 600 cases of brain tumour and other expansive intracranial lesions operated upon during the last seven years we have only a single instance of a cystic teratoma. We have considered it worthwhile to record this case because of some exceptional findings, such as the presence of a great amount of long hair within the cyst and the situation of the tumour in the cerebello-occipital region.

Case Report

A 25-year-old girl was admitted to the Institute of Neurosurgery complaining of symptoms related to increased intracranial pressure.

The symptoms started one and a half years before admission with headaches beginning in the suboccipital region and spreading upwards. There was some giddiness and sense of insecurity. The headache appeared in the mornings and increased in severity during the seven months before admission when it was accompanied by vomiting. The gait became very unsteady and there was also some lateral deviation. In the last month before admission she had noticed some irregular diplopia and progressive loss of vision.

On examination the patient was seen to be pale and thin but in fair general condition. In the scalp we found a small dimple in the occipital region, about 3.5 cm. above the external occipital protuberance in the middle line. There was a bald spot in this area the size of a finger's tip and a corresponding defect of the underlying bone. On enquiry the patient informed us that she had always had this dimple and did not connect it with the actual complaint. There was no pain or tenderness at the site. There was very marked papilloedema with secondary optic atrophy, and severe loss of vision with concentric reduction of the fields : she was barely able to count fingers at 1 metre. There was slight lateral and vertical nystagmus on conjugate deviation of the eyes. In the limbs there was moderate ataxy, tremor, and dysdiadokokinesia, if anything more marked on the left side, and the gait was unsteady. The examination otherwise was negative. Radiographs of the skull showed a small circular defect in the bone underlying the dimple in the occipital region, in addition to signs of increased intracranial pressure, e.g. convolutional thinning of the vault, enlargement of the sella, and erosion of the posterior clinoid processes.

Ventriculography revealed an obstructive lesion in the posterior fossa and a suboccipital exploration was carried out under general anaesthesia. A large cystic area was found in the upper part of the middle line of the cerebellum. The cyst contained a great amount of thick, dirty-yellow fluid and a surprising amount of hair in very long coils. The hair obtained from the interior of the cyst filled a 100 ml. cylinder and the length of the coils measured between 21 and 89 cm. (Fig. 1). Once the interior of the cyst was evacuated we saw that the tumour capsule extended deeply and upwards. Relating the finding of a congenital type of tumour with the occipital dimple present since birth, we decided to combine an occipital flap with the usual suboccipital approach in order to complete the exposure. The superior longitudinal sinus appeared deviated to the right. The invaginated occipital skin and subcutaneous tissue were dissected around the skull defect, and finally working both above and below the tentorium we removed all this tissue from the skin dimple along the fibrous band which connected it with the cerebellar mass through an aperture in the tentorium. Figure 2 is a diagrammatic representation of the anatomical arrangements.

Dr. Morales made the histological diagnosis of a very complex teratomatous tumour with epidermoid epithelium in gland-like structures, with some hair.

*Case reported to the fifth annual meeting of the Spanish Neurological Society in Barcelona in December, 1953.

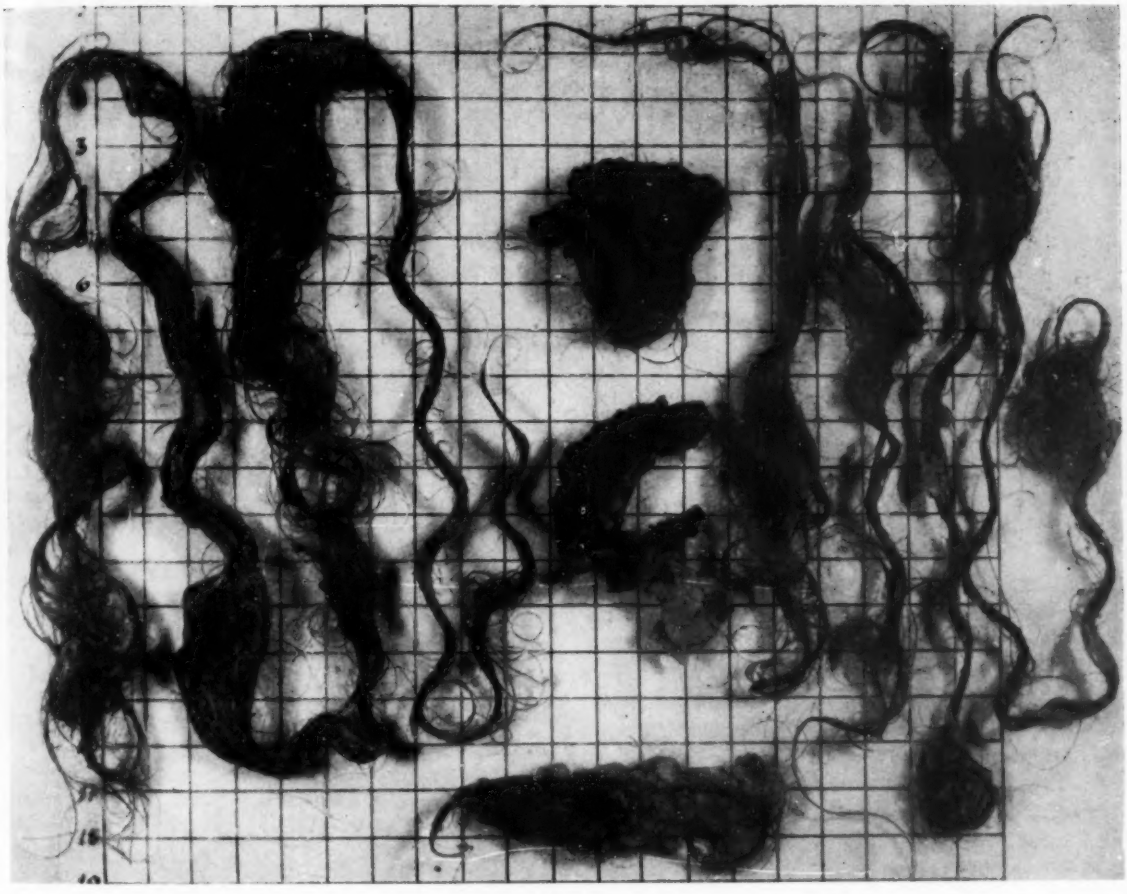

FIG. 1

Post-operatively there were no complications of significance, and frequent aspiration of subcutaneous fluid in the area of the right occipital flap was necessary only during the first few weeks. The cerebellar syndrome increased immediately after the operation but two months later it was regressing and the main residual disability was in the gait. The symptoms of increased intracranial pressure have disappeared and the papilloedema has subsided leaving a secondary optic atrophy.

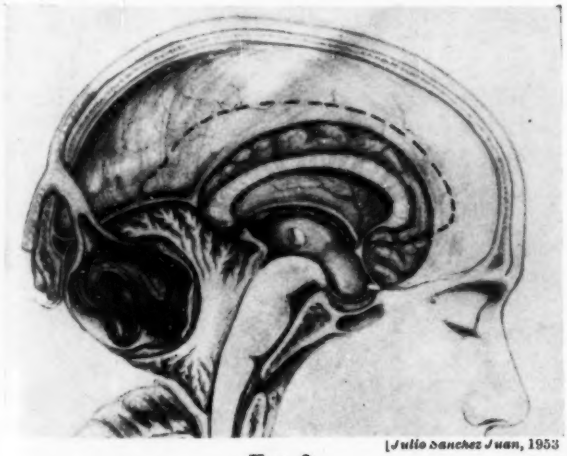

FIG. 2

Summary

A case is reported of a 25-year-old girl with a clinical syndrome of a posterior fossa tumour produced by a teratomatous cyst of the middle line of the cerebellum which contained a great amount of hair in large coils up to 89 cm. long. The tumour extended through an opening in the tentorium to the occipital region where there was a very small congenital bony defect. Combining in one stage the suboccipital approach with a supratentorial one the abnormal tissue was completely removed.

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PERIARTERITIC LESIONS OF THE CAROTID SIPHON WITH THE CLINICAL FEATURES OF A CAROTID INFRACLINOIDAL ANEURYSM

BY

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The clinical diagnosis of subclinoid carotid aneurysms is generally based on the characteristic association of two features: (*a*) pain in the first division of the trigeminal nerve; and (*b*) progressive paralysis, partial or total, of the oculomotor nerve and occasionally of the fourth, sixth, and the fifth cranial nerves. Although the symptomatic association just described is highly characteristic, it is only through the use of cerebral angiography that we are able to establish the diagnosis with certainty.

In some cases of the syndrome, arteriography may indicate the presence of a tumour in the base of the skull (the carotid siphon running a zigzag course or showing an abnormal opening of its second curve, etc.), but in others there may be a non-aneurysmal vascular process of the intracranial carotid. In this paper I wish to deal with the latter possibility, and to report a case in which the evolution and clinical condition of the patient seemed to point to the diagnosis of intracavernous carotid aneurysm, while the arteriographic examination suggested the existence of disease of the wall of the carotid siphon, and this was subsequently confirmed at necropsy.

Case Report

S. M. M., a man aged 47, was admitted to the Neurological Service of the Neurological Institute in September, 1949. His present illness began three years before, the initial symptom being pain in the left orbital region. The ache was slight but continuous for a few days. A month before the patient's admission pain was again experienced in the territory of the first branch of the left trigeminus: it became violent and continuous, and was accompanied by vomiting. During the past eight days the patient had noticed ptosis of the upper left eyelid which increased rapidly into a total left ophthalmoplegia.

Funduscopic examination revealed no important pathological changes. The visual fields were full. Visual acuity: right eye, 1; left eye, 0·5.

The third, fourth, and sixth cranial nerves on the left side were completely paralysed. The left corneal reflex was weak. Objective sensibility was normal in the region of the left fifth nerve. No disturbances of the trigeminal motor functions or defects in the remaining cranial nerves were found. The neurological examination of the trunk and limbs was also negative. Blood pressure was 140/70 mm. Hg.

Wassermann's test in the blood was negative.

The radiological examination of the skull showed only an increase in density of the small sphenoidal wing on the left side, the upper limit of which appeared ill-defined.

In the angiographic pictures, the anterior and the middle cerebral arteries appeared in their normal positions but the carotid siphon showed in the lateral view (Fig. 1) a segmentary narrowing at the level of portion C_2.

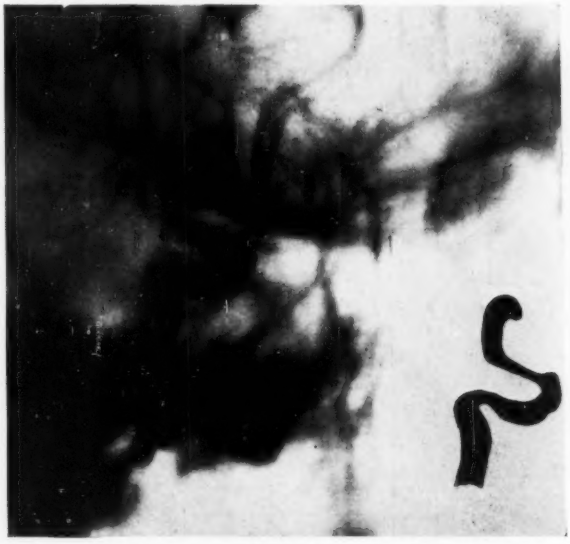

FIG. 1

This examination apparently excluded the diagnosis of saccular aneurysm or of meningioma. The existence of a malignant tumour in the base of the skull seemed

improbable since in these cases the carotid siphon ordinarily shows other changes. Although the arteriographic findings pointed to a local vascular lesion (arteritis, arteriosclerosis) this diagnosis was somewhat difficult to reconcile with the result of the neurological and radiological examinations. It was decided therefore to explore surgically the region of the sella turcica.

On September 29, 1949, under general intratracheal anaesthesia, a left transfrontal intradural exploration of the region of the optic chiasm was made. The optic nerves were short. No lesion was found either in the parasellar region, in which only slight arachnoidal opacity was discovered, or in the sphenoidal ridge. The temporal pole, the anterior part of the Sylvian fissure, and the posterior side of the great sphenoid wing were explored with negative results. The tension was still raised and suggested the possible existence of a deep tumour. However, the dural incisions and the bone and cutaneous flaps were closed.

The post-operative condition was satisfactory on the first and second days, but on the third day the patient fell into a torpor and thence into a coma, dying on October 2, 1949.

At the post-mortem examination no aneurysm was seen in the arterial circle of Willis and no tumour was disclosed in the brain or at the base of the skull. The latter presented an asymmetric shape, the sphenoid ridge and the superior edge of the petrous pyramid on the left side being on a more dorsal position than those on the right side. The cavernous sinuses were opened on both sides. On the left the intracavernous portion of the carotid was wrapped in granulomatous tissue which, however, did not completely obstruct the lumen of the sinus. This segment of the left carotid was also markedly narrowed. Altogether the curvatures of the left carotid siphon were wider than those of the right side, and its walls were excessively rigid and thick, and of a yellowish colour which contrasted with the whitish-grey of the right one.

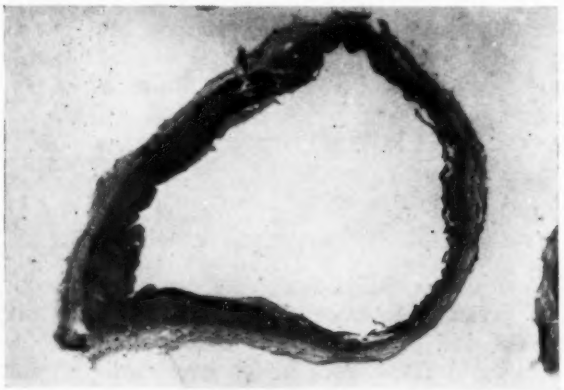

FIG. 2a

FIG. 2b

Serial sections were made of the carotid siphons in order to compare their microscopical appearance. The left intracavernous carotid (Fig. 2b) in some parts showed a thickening of the adventitia. Around it there was a cuff of non-specific granulation tissue including the adjoining nervous trunks. No endoarteritic or mesoarteric lesions were found. The right intracavernous carotid (Fig. 2a) was practically normal in appearance.

Sections were made from various regions of the hemispheres, no pathological features being observed in either the nervous tissues or in the vessels. There was obvious oedema of the cerebral tissue in the white matter of the left frontal lobe.

Comment

This report shows that periarteritic lesions of the intracavernous section of the carotid artery may bring about a clinical syndrome resembling that of an aneurysm of the infraclinoid carotid. The classic paper by Jefferson (1938) shows that the syndrome observed in this case is almost always caused by aneurysms of the anterior portion of the intracavernous carotid. This syndrome is in contrast to that of the aneurysms of the posterior third in which pressure directly on the trigeminal root affects the whole of the trigeminal sensitive territory (sometimes including the motor branch) and to that of aneurysms of the middle third where the first and second branches of the fifth nerve are reached.

Discussing the diagnosis of these aneurysms, Jefferson remarked that the cavernous syndrome may be found in connexion with syphilis, with malignant tumours at the base of the skull, with a parasellar meningioma, and also, although exceptionally, with a hypophyseal adenoma, but no allusion is made to the possibility of lesions such as those just described. The association of symptoms of the pericarotid nerves to non-aneurysmal lesions of the carotid siphon is not, however, as exceptional as might be believed.

In a case of a 63-year-old patient recently observed by me, who presented with a right hemiplegia, pains in the left half of the head, and paralysis of the left third nerve, the carotid angiography (left side) showed that not only did the anterior cerebral artery not fill, but there were irregularities in the

calibre of the siphon with many segments appreciably narrowed (Fig. 3). List and Hodges (1946) have described a case with a narrowing of the right carotid siphon (probably associated with an occlusion of the ophthalmic artery) in which a transient partial oculomotor paralysis of the right side was present. Finally, the participation of the third homolateral nerve has been noted in some cases of thrombosis of the carotid.

The pathogenesis of the oculomotor palsy of this case must be due to the inclusion of the pericarotid nerves in the inflammatory process which enveloped the carotid siphon. The carotid lumen was perfectly patent, and the lesions, being exclusively pericarotid, make the case quite different from those of carotid thrombosis.

The changes in the intima of the vascular lesion lead to the question of whether the syndrome could be related to the disease of Winiwater-Buerger. However, in the literature on Buerger's cerebral disease (Krayenbühl, 1945 ; Davis and Perret, 1947) lesions are not described which are comparable to those in this case, in which the arterial lumen was completely free of thrombosis and endoarteritic lesions were entirely lacking.

It would also be possible to classify this case as one of thrombosis of the cavernous sinus and to consider it a partial one as the sinus lumen was not totally occluded. However, the important narrowing of the siphon and the fact that granulomatous tissue gathered around it forming a periarterial cuff, suggest that the lesion originated in the arterial wall.

Ecker (1945), Chavany, Guiot, and Poloukhine (1952), and others have repeatedly observed segmentary spasms of the carotid siphon in the angiograms of intracranial aneurysms. If, in addition, we bear in mind that for various reasons the aneurysmal sac may not be visible in the angiogram, as shown, among many others, by the cases of Alpers and Ryan (1949), it can easily be realized that angiography may not be sufficient to distinguish between a case like the one submitted here and a case of aneurysm of the parasellar region.

Local or segmentary arterial narrowing must not, therefore, always be interpreted as pathognomic of a thrombo-angeitic or endoarteritic process reducing the lumen of the vessel, but only as the effect of a lesion of the wall of the artery of the most varied nature, or of merely a segmentary spasm. In this case, the calibre of the left carotid was obviously decreased in segment C_2, not by a partial obstruction of the lumen, but by the constriction of the vessel in the whole of its perimeter. The rigidity of the carotid walls shows very clearly that this narrowing was due to an organic process, whereas the arteriographic narrowing of C_2 must be referred to spasm.

FIG. 3

Summary

A case is submitted with a post-mortem report of a periarteritic process of the carotid siphon with the clinical picture of a carotid infraclinoidal aneurysm. The arteriographic examination showed only a segmentary narrowing of segment C_2 of the carotid siphon which did not differ essentially from the local vascular spasms that may be seen in cases of intracranial aneurysms.

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INTRAMEDULLARY SPINAL ABSCESS

BY

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This case of abscess within the spinal cord is reported partly because the condition is rare, but also because of the remarkable morbid anatomy revealed in this case and in some others reported. The prognosis in relation to the degree of neurological function lost before treatment is decidedly better than with epidural spinal abscess, and surgical treatment was successful in this case.

The literature since 1830 (Hart) contains reports of 43 cases, in most of which the cord lesions were revealed at necropsy. Laminectomy was first performed by Cavazzani in 1899 in a case of suppuration complicating traumatic paraplegia. His patient survived, without neurological recovery. In all, 11 cases have been submitted to operation, with four cures and one survival with paraplegia.

Case Report

A boy aged 4½ years came under our care on February 8, 1954, with a history of progressive loss of power in the lower limbs extending over a period of four weeks. The family and previous medical histories contained nothing of note except for a mild attack of pertussis at the age of 1½ years. Two weeks after the appearance of the first indications of paraparesis he developed a respiratory infection with a productive cough; the paresis then increased at a greater rate and within a few days he was unable to stand. He was admitted to a hospital elsewhere and observed for nearly a week. The paraparesis was gross, and initially of a spastic type. Double incontinence dated from the middle of this week and coincided with a lumbar puncture. The cerebrospinal fluid was yellowish; the protein content 1,000 mg. per 100 ml., and no cells. The temperature was slightly elevated, with a maximum of 101° F. A white blood count gave 10,000 per c.mm. (60% neutrophils). A Mantoux test (1 in 2,000 O.T.) was negative. The child did not complain of pain or paraesthesiae. After the paralysis became flaccid and complete he was transferred to the neurosurgical service.

On examination he was a pale, fretful child of normal bodily configuration and stature. The temperature was normal. There was a loose productive cough (sputum not examined). On general examination the only abnormality found was a moderate clubbing of the fingers. The spine was of normal appearance and not tender to percussion at any level. There was mild resistance to full flexion of the neck, which also caused some pain in the neck.

The lower limbs were flaccid and immobile but the tendon reflexes were exaggerated symmetrically and the plantar responses were extensor. The abdominal muscles were paralysed, and the abdomen protuberant. The abdominal and cremasteric reflexes were absent.

The bladder was not distended and bladder sensation seemed to be preserved in part; he was in the habit of compressing his penis until a receptacle was provided and then voided with a good stream. (It was probable that this intelligent boy had found out for himself how to remain dry, because earlier he was reported as having "wet beds".) The anus was patulous. Sensory examination was necessarily incomplete in this rather frightened child but there was certainly no area of anaesthesia and conduction of joint and vibration senses from the lower limbs was at least partly preserved.

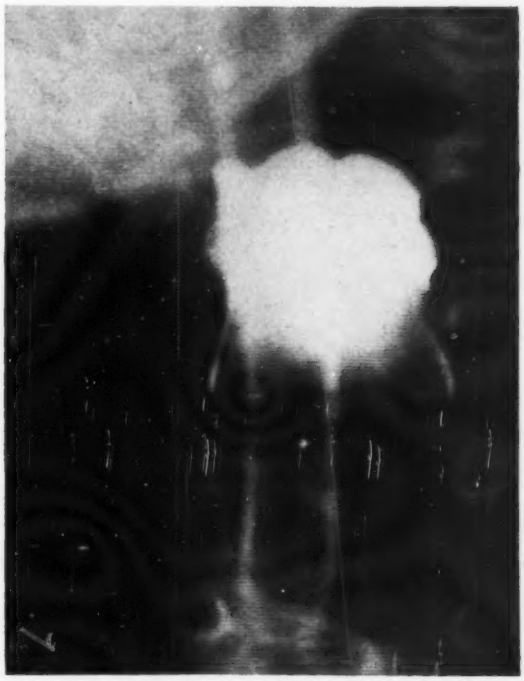

FIG. 1.—Myelogram in erect position. (The anaesthetist's intratracheal tube is also in the picture.)

Lumbar puncture showed a low pressure and a complete spinal subarachnoid fluid block. The yellow fluid clotted almost at once. Cisternal puncture yielded normal fluid. Myodil, 1·5 ml., was introduced, and myelograms (Fig. 1) in the erect position showed arrest of the medium opposite the lower border of T1 body.

On February 9, 1954, a laminectomy from T1 to T3 inclusive was performed.

Epidural fat appeared rather fibrosed but was histologically normal. On opening the tense dura the spinal cord was seen to be enlarged cylindrically for a distance of 4·5 cm. It occupied the theca completely. The expansion of the cord was rather abrupt at its upper and lower limits. The pathological segment of the cord had a rather greyish yellow tint but was resiliently soft to the touch. Small tortuous venules coursed over its dorsal surface (Fig. 2).

FIG. 2.—Operation photograph before incision of abscess.

On puncture with a sharp needle in the dorsal midline a drop of pus was aspirated and films of this, studied immediately by the bacteriologist, showed numerous long, Gram-negative rods with the morphology of *B. fusiformis*. The pus contained some degenerate cells which were not classifiable. (Cultures on ordinary media were sterile but after one week colonies appeared on Sabouraud's medium.)

A dorsal median incision into the cord for a distance of 2 cm. opened almost at once into a large central abscess cavity containing pus of cream colour with a slightly green tinge. Aspiration with the sucker was achieved with minimal contamination of the surroundings, leaving a capacious cavity 4 cm. long in the centre of the cord. The wall of the abscess appeared to be merely white matter with a few small blood vessels visible here and there running on its surface. There were no granulations and no visible fibrous tissue lining the abscess. It appeared to have lain approximately within the centre of the spinal medulla; its dorsal covering consisted of substance of the cord only about 1·5 mm. thick. It was thought that the thickness of cord lying anterior to the abscess, and perhaps laterally also, was probably rather greater. Wool pledgets soaked in 1 in 1,000 aqueous proflavine were lightly packed into the cavity and allowed to remain for five minutes. This line of treatment was chosen because of the bacteriologist's report and the appearance of the wall of the abscess which suggested a very indolent infection.

On palpating subsequently the cavity of the abscess with a blunt probe, it seemed that its upper and lower poles had been of conical shape. The appearance of the cord after evacuation of the abscess is shown in Fig. 3.

The dura was not closed. A fine rubber catheter was passed through skin and muscles close to the incision and was laid along the dorsal surface of the cord. The wound was closed in layers with silk. Sulphanilamide and calcium-penicillin powder was placed around the catheter where it emerged through the skin. This dressing was repeated daily until the catheter was removed after three complete days.

Some significant disturbances of chart readings occurred during the operation. About 20 minutes after the abscess had been drained the respiration rate rose sharply to 58 a minute, and simultaneously extrasystoles were noted, recurring every five to 10 beats for a period of 15 minutes. The pulse remained at 100 a minute. Coincidentally the blood pressure rose abruptly from 120/100 mm. Hg to 170/110. Thirty minutes later the pressure was still 160/100 mm. Hg. Respirations were 36 a minute at the conclusion.

The anaesthetic was intratracheal cyclopropane, nitrous oxide, and oxygen. A transfusion of 250 ml. of blood was given.

Streptomycin, 25 mg. in solution, was injected down the indwelling catheter for three days and the catheter was then removed. Penicillin was given in full doses intramuscularly for a week, perhaps on rather empirical grounds. The wound healed well and the chart readings were satisfactory.

Fluid aspirated from the catheter, and lumbar C.S.F.,

FIG. 3.—After evacuation of abscess.

withdrawn on several occasions, showed no indication of meningitis.

The first indication of neurological recovery, noted a week after operation, was return of movements of the toes and simultaneously the plantar responses became flexor. Muscle tone began to return in the lower limbs. Lumbar manometry about this time demonstrated reopening of spinal fluid pathways.

Two months after the operation the boy was walking with assistance, was able to stand three weeks later, and was beginning to walk unaided by the end of the third month.

Bronchograms on April 27, 1954, showed a normal tree. The clubbing of the fingers became hardly dectectable.

Discussion

This case is considered to be one of haematogenous infection in the spinal cord from a presumed pulmonary source. The organism recovered from the abscess is a common saprophyte in bronchiectasis. The patient earlier had pertussis and there was a more recent history of febrile illness. The fingers were clubbed. Bronchograms during convalescence showed no pulmonary source of infection. An opportunity was overlooked in omitting examination of the sputum in the acute stage.

The pressor disturbance and the cardiac irregularity appearing soon after evacuation of the abscess are of interest and are not unique after operative interventions on the cervical spinal cord.

Concerning the morbid anatomy of the abscess the impression was gained that the infecting organisms had been delivered into the centre of the cord and that the abscess had enlarged by separation of fibres rather than by destruction of tissue. The tracts appeared to have been flattened by benign pressure from within the cord. The degree of neurological recovery attained is supporting evidence of the benignity of the process.

Relevant points from the literature will be considered under headings.

Bacteriology.—In the 11 reported cases subjected to operation the infection was due to staphylococci, streptococci, pneumococci, *E. coli*, and actinomyces. *B. fusiformis* has not previously been reported. The type of organism was apparently not related to the prognosis but the virulence can be presumed to have been high in eight other cases with a short history and rapid onset of disability.

Morbid Anatomy.—A remarkable feature in many of the reported cases has been the length of the cord involved as disclosed at operation or necropsy. In three cases (Dubreuilh, 1886–87 ; Cassirer, 1903 ; Moersch, 1922) the whole length of the cord was found at necropsy to be implicated ; in 10 cases about half of the cord harboured an abscess. As might be expected the abscesses were not extensive in the patients who survived but at least three segments of the cord were affected in all of them.

Another noteworthy feature is the central location of the abscess in many instances (Fig. 4), enlargement taking place longitudinally, as might perhaps be anticipated in a cylindrical structure composed peripherally of fibre tracts and lying within a firm

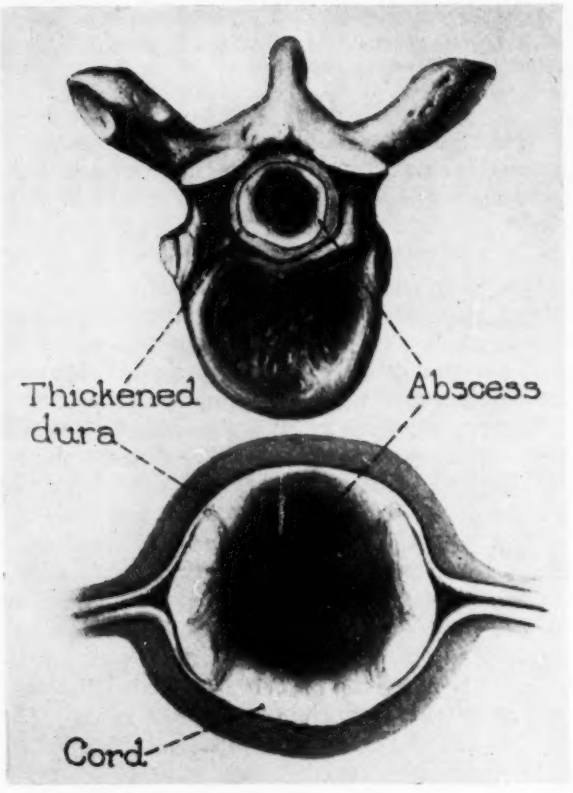

FIG. 4.—Illustration from Woltman and Adson's paper in *Brain*, reproduced by courtesy of the publishers.

membranous tube of dura mater. The process appears to be what might be termed a " pyosyrinx " of the cord.

All levels of the cord have been implicated, with a predilection for the thoracic part which is understandable if the length of many of the abscesses is borne in mind.

Aetiology.—Endocarditis with septicaemia has been responsible for terminal infections of the cord in five of the reported cases. The lesions were of pathological rather than of clinical importance. Infection came from the lung in five other cases, all ending fatally. In the group of 20 cases of haematogenous spread the abscesses were multiple in the cord in eight and solitary in twelve.

Direct spread to the cord from neighbouring foci, such as juxtarenal infection or compound vertebral injuries, has occurred in 16 cases. In addition to these 36 cases there have been seven cases of primary abscess of the cord.

Experimental Observations.—It is noteworthy that as early as 1899 Hoche was successful in producing abscesses experimentally in the spinal cord. Using finely particulate emboli such as pollen and clay powder he had earlier produced infarctions in the spinal cord in dogs by injection into the aorta. He found that bacteria free in the blood stream rarely caused intramedullary suppuration unless the experimental emboli were present simultaneously. He concluded that emboli had to be very small to enter the intramedullary arteries and that when they did so they were arrested, mainly in the grey matter. The arteries nourishing the interior of the cord are given off perpendicularly from the parent trunks and he postulated that this circumstance might contribute to the rarity of abscess of the spinal cord in man. Hoche stressed the importance of trauma to the spine in determining the level of infection in the cord, but it is evident from the literature that injury has been an unimportant factor in man.

Treatment.—Laminectomy has been performed in 11 of the reported cases, all with solitary abscesses (Cavazzani, 1899; Hitchcock, 1917; Woltman and Adson, 1926; Nonne, 1926; Sittig, 1927; Abeshouse and Bogorad, 1935; Urechia, 1935; Walker and Dyke, 1936; Altenburger, 1937; Alessi and Fasiani, 1940; Ameli, 1948). Five patients survived and of these four were cured. Dorsal median incision of the cord was practised by Woltman and Adson in a case of idiopathic indolent staphylococcal infection of the thoracic cord, and by Walker and Dyke in a case of congenital dermal sinus in the lumbar region infected by pneumococci and coliform bacilli. Aspiration alone was effective in the hands of Alessi and Fasiani in a case of septicaemia, several pyogens being recovered from the abscess. Aspiration with instillation of antibiotics was used by Ameli at two explorations in his case of metastatic abscess of the lower thoracic cord.

Surveying the histories in the cases which recovered one is impressed by the considerable period over which neurological symptoms existed without permanent and complete damage to the cord. The patient of Woltman and Adson had a sudden paraplegia which recovered spontaneously over four months, but recurred more than a year later. She lay almost completely paraplegic for eight months before operation, yet was able to walk again. Alessi and Fasiani's recorded paraparesis advanced over a period of seven weeks, and Walker and Dyke's patient was paraplegic for a month. Ameli's patient was paraplegic for three weeks before the first aspiration.

It is surprising to find that the prognosis in spinal epidural abscess is potentially much worse than with intramedullary abscess, if presenting as a syndrome of disease of the spinal cord. Hulme and Dott (1954) came to the conclusion from the literature and from their own material that once conduction in the spinal cord becomes seriously affected in cases of spinal epidural abscess it is already too late for successful treatment, even though in some acute cases the opportunity be lost by only a matter of hours. In contrast, almost complete paraplegia had been present for three days in our case of intramedullary abscess, and for much longer in other published cases in which recovery ensued after operation. The patients in all four of the successful reported cases were able to walk within three months of operation. Presumably the indolence of the infection contributed to the good results in these cases and in the one described here.

Summary

A case of intramedullary abscess in the thoracic part of the spinal cord is described. The infecting organism was *B. fusiformis* of presumed but unproven pulmonary origin. Laminectomy and drainage of the abscess was successful.

We are indebted to Dr. Beryl Corner, F.R.C.P., for referring the patient; to Dr. J. G. C. Spencer and the Bristol University Department of Bacteriology for their investigations; to Dr. L. Mandelbaum and Mr. E. Dutton for assistance with translations; and to Mr. L. G. Banham for the photography. The illustration Fig. 4 appears by courtesy of the editor of *Brain*.

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THE AUGUST (1954) ISSUE

The August (1954) issue contains the following papers :—

The Toxic Effects of Tri-ortho-cresyl Phosphate on the Nervous System : An Experimental Study in Hens. J. B. Cavanagh.

Mental Disturbances in Tuberculous Meningitis. Moyra Williams and Honor V. Smith.

Repetitive Discharges from Human Motor Nerves after Ischaemia and Their Absence after Cooling. William Cobb and John Marshall.

Angiographic Diagnosis of Vertebral Artery Thrombosis. A. van der Zwan.

A Contribution to the Genetics of Gargoylism. Robert C. Cunningham.

A Persisting Change in Palmar Sweating Following Prefrontal Leucotomy. Alick Elithorn, Malcolm F. Piercy, and Margaret A. Crosskey.

The Effect of Cardiazol Convulsions on the Distribution and Activity of Some Phosphatases in the Area Postrema of the Rat. Jorge A. Insua and D. Naidoo.

A Case of Clinical Juvenile Amaurotic Idiocy with the Histological Picture of Alzheimer's Disease. Aa. Christie Löken and K. Cyvin.

Symptoms of Anxiety and Tension and the Accompanying Physiological Changes in the Muscular System. Peter Sainsbury and J. G. Gibson.

An Intraspinal Dermoid Cyst Associated with Another in the Ovary. B. Ramamurthi and V. C. Anguli.

The Production of Gamma-globulin in the Central Nervous System. E. O. Field.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12s. 6d.

BOOK REVIEWS

Peripheral Nerve Injuries, 2nd ed. By Webb Haymaker and Barnes Woodhall. (Pp. xv + 333 ; 272 illustrations. 35*s*.) Philadelphia and London : W. B. Saunders Company. 1953.

The authors of this book have with great efficiency collected available published information on the diagnosis of nerve injuries and have constructed thereby an excellent reference book on diagnosis. The book is almost entirely concerned with war wounds, and the classical studies which were published following both world wars are fully acknowledged and made use of. There are no fewer than 272 illustrations. The anatomical diagrams are unusually clear. The clinical methods advised for testing each muscle are illustrated by line drawings, most of which are excellent. In addition, the authors have acquired from the Armed Forces Institute of Pathology photographs of patients illustrating nearly every variety of nerve injury.

It is perhaps surprising that this book is concerned almost exclusively with diagnosis, and most readers would welcome a few chapters on the war-time experience of treatment. Some consideration of occupational pressure and traction palsies would also be useful. This is, however, a remarkably thorough and useful reference book.

Die Halswirbelsäule : Pathologie und Klinik. By Gerhard Exner. (Pp. 140 ; 42 figures. DM. 21.60.) Stuttgart : Georg Thieme Verlag. 1954.

This study provides a wealth of information about the cervical spine in health and in disease. First the normal anatomy and physiology are considered in great detail, then the congenital anomalies are described, and lastly over two-thirds of the book is concerned with pathological processes and the diseases and symptoms which may result from them. Disc degenerations are considered in relation to various brachial syndromes, but there is no consideration of the myelopathy occurring in relation to cervical spondylosis which has been considered so much recently in neurological literature. The absence of an index limits the book's value for reference, and the references given are not easily correlated with the text as the titles of the papers are not provided.

The Basis of Clinical Neurology, 3rd. edition. By Samuel Brock. (Pp. xii + 510 ; 124 figures. 54*s*.) London : Baillière, Tindall and Cox. 1953.

This book presents a great mass of information which provides a useful source of reference to the student of neurology. Apart from a summary of existing knowledge of anatomy and physiology, there are scattered, and at times somewhat disjointed, references to clinical problems. This book should prove useful to many, but like many textbooks the author provides little critical comment on the material presented and fails, for example, to stress the challenging gaps in present-day knowledge. Thus the book is useful but uninspiring.

The Painful Phantom. By Lawrence C. Kolb. (Pp. 50. 11*s*.) Oxford : Blackwell Scientific Publications ; Springfield, Illinois : Chas. C. Thomas. (American Lecture Series.) 1954.

This lecture describes much of what has been written about phantom sensations in medical literature.

The author admits that some pain in a phantom limb may have a physical cause but has come to conclude that " among the majority of amputees this symptom is psychologically maintained". Here, however, his argument becomes highly speculative, and the discovery of a certain type of psychological response in relation to an amputation is taken to be evidence that this factor explains the persistence of pain, without there being control studies on amputees without pain. It may be pointed out that local anaesthesia of the stump temporarily relieves many phantom pains, and the analysis of the causes of this type of pain cannot be profitably discussed without careful study of any abnormal impulses travelling up from the neuromata in the stump, and the effects of adequate nerve blocking. The author also considers that the failure of surgical procedures, such as nerve section, provides evidence of pain being psychologically maintained. This is, however, a fallacy, for a severed nerve can act as a false synapse so that nerve section may even increase the up-going impulses.

All will agree that the psychological factor in painful phantoms may be all-important and merits the most careful study, and in this regard this lecture is helpful.

Modern Clinical Psychiatry, 4th ed. By Arthur P. Noyes. (Pp. viii + 609. 35*s*.) Philadelphia and London : W. B. Saunders Company. 1953

The latest edition of this standard textbook is especially helpful as a comprehensive statement of modern psychodynamics applied to clinical psychiatry. It is well documented, and the chapters on causation and treatment provide a sound account of viewpoints and practices that are widespread in American psychiatry. Clinical descriptions are presented according to the classification of the American Psychiatric Association. Thus, disorders associated with discernible brain disturbances and mental

deficiency are dealt with before the more common affective, schizophrenic, and psychoneurotic disorders, though it is chiefly to the latter that the author applies his consolidated psychodynamic conceptions. This rather breaks the sequence of his story, as it were, but it does not detract from the usefulness of the book as a work of reference in the psychobiological and clinical fields, which will be valuable and instructive to the specialist in training. More advanced readers will discern with interest subtle differences of approach that appear to pervade American and British psychiatry at the present time.

The Psychiatrist : His Training and Development. (Pp. viii + 214.) Washington : American Psychiatric Association. 1953.

This book is the official report of a Conference on Psychiatric Education held at Cornell University in 1952. This conference was concerned primarily with the training of psychiatrists as specialists, whereas a similar conference in 1951 was concerned with the psychiatric education of medical undergraduates.

This is an enlightening book, and although its structure does not make it very easy for the reader to find his way about in it, and there is a certain tendency to repetitiveness which can hardly be avoided in such a presentation, it covers the field of psychiatric specialist training in a most adequate, factual, and constructive way. On this account alone it would repay study by all those who are concerned in the training of psychiatrists ; but it goes rather further and deals with such interesting topics as the psychiatric education of the general physician and the extension of psychiatric services into the public health field, as well as providing many facts about the numbers and work of psychiatrists, psychiatric nurses, psychologists, and social workers in relation to the needs of given populations.

Curso de Psiquiatriá. By Honorio Delgado. (Pp. 513.) Lima : Imprenta Santa Maria. 1953.

This dignified and thoughtful exposition of psychiatry rests on a foundation of learning which is nowhere obtruded on the reader but can easily be discerned. Intimately acquainted with the profuse German literature, and attentive to every new development in psychiatry, Professor Delgado preserves a critical detachment which gives his account perspective and sobriety. The first half of the book deals with psychopathology on classical lines : abnormalities of perception, thinking, feeling, instinct, will, consciousness of self, time-appreciation, memory, attention, awareness, and intelligence have each a chapter. Slightly scholastic in its orderliness, it is rational rather than stimulating. The second part, on the individual disorders, is an admirable clinical account, well arranged and up to date, which bears out the author's declared intention to keep free in his outlook from the influence of " professional routine which paralyses and of theory which blinds ". The dynamic or psychoanalytic point of view receives comparatively little attention.

This is an unusually well integrated text, clearly the product of one man who has a coherent body of experience and a philosophical background.

Group Psychotherapy : Studies in Methodology of Research and Therapy. By Florence B. Powdermaker and Jerome D. Frank. (Pp. 615. 43*s*.) Oxford University Press (London : Geoffrey Cumberlege). 1953.

There is so little established knowledge about group psychotherapy that this candid and rather elaborate account of an experiment in it is welcome. The 23 doctors conducting it had no common fund of training and experience in the method before the investigation began, so that the difficulties attending any assessment of the processes and the efficacy of individual psychotherapy appear with even greater prominence here. By regular discussions, however, between the psychiatrists and the psychologists and social workers concerned, those taking part went through a mutual training. The chief investigators concluded that in these circumstances efforts at statistical treatment of material obtained by a carefully designed experiment would be premature. Their findings therefore tell almost nothing about the therapeutic efficacy of the group method, the indications for its employment, or the most satisfactory techniques. They are, however, suggestive about what happens in group dynamics, especially where the chronic schizophrenic groups are in question, and there is much informative material about the methods of recording and " situation analysis " appropriate to such an inquiry. The work is in two parts, the first dealing with outpatients, chiefly neurotic, and the second with chronic schizophrenics in a mental hospital.

Rorschach Interpretation : Advanced Technique. By Leslie Phillips and Joseph G. Smith. (Pp. 385.) New York : Grune & Stratton. 1953.

A Clinical Approach to Children's Rorschach. By Florence Halpern. (Pp. 270. $6.00.) New York : Grune & Stratton. 1953.

These two books take for granted the trustworthiness of the Rorschach method of evaluating personality. They are, it is true, mildly apologetic : Drs. Phillips and Smith admit that the relationships they assert between test results and behaviour have not been corroborated, but represent what they oddly call " guessed-at laws " ; Dr. Halpern defends her many unvalidated statements by pointing out that it would take a very long time to validate them, or that there are not as yet methods for doing so. This is very weak ground, and the psychologist or physician who is sceptical of the bold interpretations made from ink-blot responses will remain so when assured by these authors that " the method works ". It is increasingly recognized, on the contrary, that the method does not work in diagnosis of mental disorder, because of overlap, and that different experts arrive at different judgments of personality from the same protocols. The two books are intended as clinical manuals, and they appeal to the authors' experience for their

authority. This experience is considerable, but its fruits are not easily communicable, nor necessarily correct. In both books there is lacking a coherent theory of personality with specified and unequivocal vectors; consequently the personality characteristics inferred are often isolated traits or vague tendencies. The drawbacks of the books are, however, those inevitable in any Rorschach manual: psychologists or psychiatrists who want to use the test for clinical purposes will get practical guidance from them which is detailed, well arranged, and resourceful.

Treatment of Mental Disorder. By Leo Alexander. (Pp. xi + 507; 143 figures. 50*s*.) London and Philadelphia: W. B. Saunders Company. 1953.

In any American book on the pathology or the treatment of mental disorder, the most significant indicator is usually the author's attitude to psychoanalysis. Dr. Alexander is very cautiously critical: neither swimming against the stream nor setting up a dam, he hugs the bank and utters temperate warnings to bolder spirits. His own boldness lies in the application of physical methods, especially E.C.T. Here he is in his element, and the bulk of the work is devoted to the technical and clinical minutiae of convulsant treatment. The combination of physical treatment and dynamic psychotherapy is the subject of an interesting chapter, and there are further chapters on the treatment of alcoholic addiction, toxic states, and the "organic" mental syndromes. A final chapter, on "Frontiers for New Research and Development," contains unexceptionable precepts regarding the statistical evaluation of therapeutic efficacy and the study of neural mechanisms and autonomic balance. The book is restrained in style, clear in all its therapeutic injunctions, and as erudite and factual as its author's extensive training in neurology, morbid anatomy, and psychiatry would lead one to expect.

Psychotic and Neurotic Illnesses in Twins. By Eliot Slater, with the assistance of James Shields. (Pp. 385. 21*s*.) London: H.M.S.O. Medical Research Council Special Report Series No. 278. 1953.

This report is a model of genetic research by the twin method. An unselected series of surviving pairs of twins, one of whom was known to have a mental disturbance, was taken from a number of mental hospitals and the Maudsley Hospital. Case histories were studied and both twins examined to determine points of likeness and unlikeness. There were 67 uniovular and 224 binovular pairs. In addition to data of general significance in the study of heredity (including statistical analysis of the method of diagnosing uniovularity from fingerprints), findings of importance for the aetiology of mental disorder were obtained. The personalities of uniovular twins were very similar, except that energy of character might be pronounced in one and inconspicuous in the other member of the pair. When one twin had schizophrenia, there was very much more likelihood that the other would have it when they were uniovular than when binovular, in the proportion of 76 to 14. Affective illness also was commoner in both when they were uniovular. In psychopathic and neurotic states environmental causes of illness could be inferred to play a large part.

The impartiality and thoroughness of this study make it an important contribution to the aetiology of mental illness. Dr. Slater has not restricted himself to assessing or asserting the role of heredity but has combined his clinical with his genetical approach to yield a broad view of the relative importance, and the interplay, of inheritance and environment. Many interesting pointers to further research emerge. It is obvious that differences between uniovular twins, which must be studied closely in the individual life stories, are as illuminating as similarities, upon which so much more attention was formerly bestowed; consequently the full and classified case histories which constitute Part II of the report are both necessary and profitable for an adequate survey of the evidence.

Bodily Physiology in Mental and Emotional Disorders. By Mark D. Altschule. (Pp. 228. $5.75.) New York: Grune & Stratton. 1953.

The physical changes recorded in mental illness are so numerous and seemingly discrepant that an organized survey of the facts has been much needed. Like most writers on psychosomatic relations Dr. Altschule is biased, but his bias, unlike theirs, is against speculation or symbolic interpretation and strongly towards laboratory observations. The facts which he has laboriously assembled and classified are presented tersely; his comments on them are critical, cautious, and sometimes enlivened with a caustic humour. He detests flatulent writings, and holds it deplorable but "not surprising that a system of thought as undisciplined as psychiatry should often follow the quick, short way of flights of imagination rather than the long, difficult road of observation in exploring the jungle of mental disorder. . . . Informed ignorance is to be preferred to misguided certainty." His book is salutary as a corrective to loose assumption, and a classified storehouse of findings. The book is divided into chapters according to physiological and chemical systems, and the chapters are subdivided into relevant effects of emotion in normal persons, phenomena of neurotic states, and of manic-depressive, involutional, and schizophrenic psychoses. It is a pity that Dr. Altschule has not inserted compendious chapters detailing the assured findings in each of the psychoses; for the most part he writes as though the psychoses must be lumped together, and it is not easy to discover what physiological changes are different in schizophrenia from those of affective psychosis. The subject index could be made fuller with advantage—such important words as schizophrenia and stupor do not occur as main headings—and an author index would be a convenient addition. The book is so useful, however, that it is greatly to be hoped Dr. Altschule will keep it up to date by subsequent editions.

Neurosenfrage, Ursachenbegriff und Rechtsprechung, 2nd ed. By W. Schellworth. (Pp. xvi + 98. DM. 9.–.) Stuttgart : Georg Thieme Verlag. 1953.

The first edition of this work appeared in 1939, apparently as a somewhat polemical work, designed to draw attention to conflicts between medical and judicial viewpoints on the subject of the compensation-neurosis. In his foreword to the second edition the author states that the polemical character of his dissertation has now been allowed largely to lapse. However that may be it is clear that in Germany as here there is still but little understanding on the judicial bench of many fundamental medical concepts.

The most important of these is that of causation. Schellworth distinguishes between *Ursache* (cause) and *Grund* (reason). The first leads, by processes which are to be understood biologically and medically, to effects which may indeed constitute disease or illness. The latter leads, by processes which are to be understood psychologically, to complaints perhaps but not to illness. Thus at one time there was a spate of telephone accidents in Germany ; switchboard operators, startled by sudden crackling noises in their ears, complained of symptoms and received compensation. When it was made officially known that the noises were harmless and symptoms following them would not be compensated, such cases ceased to occur. Compensation neuroses are not illnesses at all.

This is the central theme of the work, and it is argued out with all thoroughness and with a full examination of the opposed lay, common-sense viewpoint as exemplified in judicial decisions and precedents. A legal reader could and should find it of great assistance in clarifying his ideas. Nevertheless, from the psychiatric viewpoint the discussion seems inadequate. Compensation-neuroses are dealt with as something *sui generis*, when in fact they constitute only a special case of neurotic illness in general, in the causation of which motivation plays an infinitely variable role, sometimes decisive, sometimes less important, sometimes of minor or negligible significance. To the psychiatric, as opposed to the forensic problems, this book contributes but little.

Endocrine Disorders in Childhood and Adolescence, 2nd ed. By H. S. Le Marquand, F. H. W. Tozer, and W. J. Tindall. (Pp. xiii + 332 ; 90 illustrations. 32*s.* 6*d.*) London : English Universities Press. 1954.

The second edition of this work appears more than a decade after the first, and during that time many fundamental advances have been made in the study of the physiology of the endocrine glands. On the clinical side also, new syndromes have been defined and older diseases and syndromes reformulated in the light of new knowledge. The authors have therefore revised large sections of this book, and have had the help of a third collaborator in re-writing the section on physiological aspects. A particular merit of this work is the opportunity for prolonged observation of cases and their families that the authors have had by reason of practising in a county town with a relatively stable population. Thus many of their descriptions give a long-term view of the disease, which is most useful. This is well shown in the chapter " The Natural History of the Fat Child ", where the story is in fact traced beyond childhood and adolescence into adult life.

Chapters on the adrenal gland, the gonads, thyroid, and parathyroids give succinct descriptions of the syndromes involved. Diabetes is fully discussed and the special problems of control in children are excellently dealt with. A brief description of Selye's theories of the adaptation syndrome is given and the use of A.C.T.H. and cortisone is mentioned. However, work in this field is still developing rapidly and no book can be expected to contain the latest information. The references to original papers are well selected and contain both classical and recent work. The book has some excellent tables of standard measurements of physical development and also a most useful one of proprietary hormone preparations.

The Living Brain. By W. Grey Walter. (Pp. 216 ; illustrated. 15*s.*) London : Gerald Duckworth. 1953.

This book is admittedly a popular exposition of the findings of electro-encephalography and some of its experimental applications, so that the reader trained in a scientific discipline must contain his irritation at the arresting rather than accurate use of language employed. Even so, the author's fairly frequent excursions into somewhat superficial analogies seem unnecessary and, for his intended audience, at times misleading. In the first chapter entitled " Lords of the Earth " there is a brief discussion of the evolution of the nervous system. The dinosaur's possession of a lumbar enlargement to the spinal cord comparable in size and, possibly, complexity to its intra-cerebral brain, is likened to " a physical prototype of schizophrenia ". The importance of homeostasis is emphasized, and the mechanical calm which this may allow to the activity of the brain is considered to reflect such states as nirvana, Yoga contemplation, or " the peace that passeth understanding " aimed at by religion and mysticism. In succeeding chapters a brief history of the development of electrophysiology leading to the discovery by Berger of the E.E.G., and of cerebral physiology, both on the Pavlovian and Sherringtonian side, is given. The author allows himself a brief aside on the possible ill-effects on brain mechanisms " of the popular arts of today ". " Heaven only knows ", he says, " what mutations this titillation may in time promote . . .". He then discusses at some length the various patterns of E.E.G. activity that have now been recognized and the ways of influencing them by such stimuli as light flashes of carefully controlled frequency and intensity. The association of particular types of E.E.G. pattern with such personality traits as aggressiveness and delinquency is also considered. Here the author is reviewing work that he has himself pioneered and is interesting and informative : though those with access to the original literature may at times doubt how firmly established are some of the facts he presents. Also of special interest is his description of the electrical " animal " (christened " *machina speculatrix* ")

he has constructed to show apparently "purposive" behaviour to certain limited stimuli: and his postulation of seven essential steps in electrical processes in order to achieve "conditioning" or "learning" in such an "animal". The E.E.G. changes in sleep and hypnosis are contrasted. Finally, in "The Brain Tomorrow" some implications, particularly of the E.E.G. correlates of personality, for education and medical treatment are considered. Three appendices give details of electrical modes for nerve impulses, "machina speculatrix" and a "conditioned reflex analogue".

In general this book represents much the same viewpoint as that of the school of "cybernetics" in America. Neurologists and psychiatrists will find parts of it of great interest, as giving a summary of recent work on the borderland of electroencephalography, but they should take even this with a grain of salt. In other parts they may find much banal and somewhat superficial speculation which will only irritate. This is perhaps not entirely irrelevant criticism, even considering the author's avowed intention of popular appeal.

Physiological Foundations of Neurology and Psychiatry. By Ernst Gellhorn. (Pp. 556; illustrated. 68*s*.) Oxford University Press (London: Geoffrey Cumberlege). 1953.

It would be a notable achievement if any book could live up to the promise of such a title as this. Dr. Gellhorn does not attempt it but has the more modest (though still very exacting) aim of expounding those physiological relations which his own work has made familiar to him. As his work has been so widespread and vigorous—the bibliography lists references to a hundred articles and books of his—it gives ample scope for covering authoritatively much territory that is important for neurology and psychiatry. The sections dealing with movement, autonomic function, and integration are the most detailed: Part six, which concludes the volume, is concerned with the applications of physiological knowledge to the pathology and treatment of mental disorder, especially schizophrenia; it is tentative, and (as in the chapter on carbon dioxide therapy) learnedly inconclusive. Gratitude to Dr. Gellhorn for collecting and synthesizing so much material is compatible with regret that he did not narrow his field of discussion to a stricter review of autonomic and humoral regulation of neural functions.

The Autonomic Nervous System, 4th ed. revised. By Albert Kuntz. (Pp. 605; 94 figures. 80*s*.) London: Baillière, Tindall and Cox. 1953.

Professor Kuntz in this fourth edition has considerably revised and added to this work. It is a difficult task to cover all aspects of the autonomic system in a volume of some 600 pages, and it may be doubted whether it is now a profitable attempt. The information available justifies separate publications on anatomical, physiological, and clinical aspects. The present work is inevitably of uneven merit. Physiology fills the main part of the book and is excellently done. Anatomy, embryology, and histology are not so fully treated. Finally the clinical aspects are discussed. Here, although the author has been at pains to inform himself about the recent literature, the clinician may get the impression of a catalogue of facts and findings rather than a balanced assessment based on experience. Nevertheless, the book remains a useful introduction to the subject, especially for the pre-clinical student. The references are full, the index good, and a nice historical perspective is maintained with regard to the earlier physiological work.

Human Neuroanatomy, 3rd ed. By Oliver S. Strong and Adolph Elwyn. (Pp. xii + 482; 357 figures. 57*s*. 6*d*.) London: Baillière, Tindall and Cox. 1953.

This book covers briefly the anatomy of both peripheral and central nervous systems in man, with their coverings and blood supply. To have collected and organized this material within the space of 500 pages is itself no mean achievement, and it is not surprising that some parts of the work are less adequate than others. On the whole, the peripheral nervous system, although clearly described in the text, is less well illustrated than the central. Here it is good to see recognition of the comparatively small contribution that the Betz cells make to the pyramidal tract. The diencephalon is particularly well described and clearly illustrated, both in photographs and diagrams. In the cerebral hemispheres the drawing of the hippocampus brings out well both its anatomical relations and the reason for its name. The references are adequate and up to date, and the index thorough. In general neurologists will find this a useful small reference book which is reasonably comprehensive, confined to the human nervous system and so unencumbered by references to the lower mammals which are of doubtful homology and sometimes therefore quite misleading.

Traité Technique de Tomographie Osseuse. By Robert Herdner. (Pp. 408; 338 figures. Fr. frs. 4,000.–.) Paris: Masson et Cie. 1954.

This is an excellent book dealing with the tomographic anatomy of the skull and should form a very useful asset to any radiographic or anatomical library. The author deals exhaustively with the many different techniques he has employed to show different structures. The quality of the pictures obtained is excellent. Unfortunately, most of the illustrations have been taken from radiographs made from a dry skull and there is little indication of the application of this work in clinical practice. The author also makes some references to the use of tomography in the examination of the spine and sternum.

Comparative Psychology. Edited by Calvin P. Stone. 3rd ed. (Pp. 525; 91 figures, 722 references. 50*s*.) London: Staples Press. 1953.

This third edition of a standard work on psychological studies of animals, which first appeared in America in 1951, has now been published in this country. The 13 authors have aimed at a comprehensive survey, which,

however, suffers from the omission of all but a few European studies. The important work of Lorenz and Tinbergen receives no mention, and there is no reference to the work of Otto Koehler on counting and symbolism. These and other lacunae weaken the value of the critical discussion at many points.

The ground covered by the book includes a historical review, maturation and instinctive functions, motivation, internal secretions, learning, discriminative behaviour, individual differences, social aspects of behaviour, and abnormal behaviour. Readers of this journal will be particularly interested in the chapters on " Internal Secretions and Behavior ", " The Neurology of Learning ", and " Abnormal Behavior in Animals ". The chapter on " The Neurology of Learning ", by Donald G. Marquis is disappointing. Although he deals with the effect of electric shocks on learning (p. 307). we have to wait until Patton's chapter on " Abnormal Behavior " for an account of the experiments on habit-reversal, and neither author discusses a possible human parallel, the amnesia for recent events after electro-convulsant therapy. Neither Marquis nor K. W. Spence, in his chapter on " Theoretical Interpretations of Learning ", discusses the various electronic learning models. In his chapter on " Abnormal Behavior ", Robert Patton describes methods of inducing " experimental neurosis " in various species, draws attention to the misleading implications of the term, and reports experiments in which it was found that subsequent thyroidectomy, injection of cortin, and bilateral frontal leucotomy reduce symptoms in sheep. He maintains that the daily imposition of restraint and relinquishing certain types of spontaneous behaviour, as well as the monotonous repetition of certain patterns of stimulation, contribute to the retreat into abnormal behaviour, but draws no parallel with the human subject in an unsatisfactory social or occupational environment.

In short, the weaknesses of the book are mainly those of omission, and the medical reader will find much material relevant to clinical problems.

Commentary on the Effect of Electricity on Muscular Motion. By Galvani, translated by R. M. Green. (Pp. xx + 97 ; illustrated. $4.00.) Cambridge, Massachusetts : Elizabeth Licht. 1953.

This is the first English translation of Galvani's famous treatise " *De Viribus Electricitatis In Motu Musculari Commentarius* ", published in 1791 in the proceedings of the Bologna Academy of Science and Arts. The work was a landmark in the development of electrophysiology and it is perhaps appropriate that this era should see it made accessible to that large audience whose debt to Galvani is considerable. Although the translation is not always felicitous, the meaning is always clear. The commentary itself gives a detailed description of his observations and experiments and is of special interest as illustrating his methods of thought and approach to problems which are also exemplified in an exchange of letters between Carminati and Galvani included here, together with a dissertation on the development of the theory of animal electricity by Galvani's nephew. These three items reproduce the text of a small volume published by the nephew a year after the original commentary had appeared, and add to the historical interest of the book. In addition there is a brief introduction and biographical sketch by Professor Pupilli, the present director of the Institute of Human Physiology at Bologna.

The Psychology and Psychotherapy of Otto Rank. By Fay B. Karpf. (Pp. 129. $3.00.) New York : The Philosophical Library. 1953.

Rank's later views had little of the limelight which was once directed on his birth traume theory of the genesis of anxiety. After the rupture between him and the Freudian school he developed and modified his dynamic concepts, so that they were ultimately very different from the psychoanalysis of which he had once been a brilliant exponent. He put much stress upon will and creativity as central agents in psychotherapy. He never succeeded in systematizing his ideas or settling his therapeutic techniques : consequently his vogue among psychiatrists was weak, but with psychiatric social workers in the United States he became a powerful influence, especially in Philadelphia. The author of this admiring but not adulatory account was a close associate of Rank's ; her well-informed presentation of his teaching and practice will be found instructive by those desirous of closer acquaintance with the aberrant offshoots of psychoanalysis.

Gynakologische Organneurosen : Einführungsvorlesungen in die Psychosomatik. By Hans Roemer. (Pp. 190. D.M.13.50.) Stuttgart : Georg Thieme Verlag. 1953.

The spread of " psychosomatic " interest has reached gynaecological clinics, rich as they are in neurotic complaints and physical manifestations of emotional disturbance. Professor Roemer says, for example, that in his experience such disorders as dysmenorrhoea without underlying physical disease account for 10 to 20% of the time spent by a gynaecologist in consultations and out-patient work. His lectures are simple in language, and assume a greater simplicity in the mechanism of neurotic illness than psychiatrists can accept, but he is not writing for psychiatrists and the straightforward advice he gives to gynaecologists regarding the investigation and management of most of the women who come to them with predominantly psychogenic symptoms can be easily understood and readily applied, with good results.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Diencephalon : Autonomic and Extrapyramidal Functions. By Walter Rudolf Hess. (Pp. 79 ; 33 figures. $4.00) New York : Grune & Stratton. 1954.

Endokrinologische Psychiatrie. By M. Bleuler. (Pp. 498; 30 figures. DM. 46.50.) Stuttgart: Georg Thieme Verlag. 1954.

Prefrontal Leucotomy and Related Operations: Anatomical Aspects of Success and Failure. By Alfred Meyer and Elisabeth Beck. (Pp. 60; illustrated. 10*s*. 6*d*.) Edinburgh: Oliver & Boyd. 1954.

An Introduction to Physical Methods of Treatment in Psychiatry, 3rd ed. By William Sargent and Eliot Slater; chapter on *Treatment of the Epilepsies* by Denis Hill. (Pp. xix + 351. 20*s*.) Edinburgh: E. & S. Livingstone. 1954.

Sigmund Freud: On Aphasia. Translated by E. Stengel. (Pp. 105. 12*s*. 6*d*.) London: Imago Publishing Co. 1953.

The Origins of Psycho-Analysis. Sigmund Freud's letters to Fliess. (Pp. 445. 30*s*.) London: Imago Publishing Co. 1954.

Intracranial Gliomata. By John Penman and Marion C. Smith. (Medical Research Council Special Report Series No. 284). (Pp. 69. 5*s*.) London: H.M. Stationery Office. 1954.

Connections of the Frontal Cortex of the Monkey. By Wendell J. S. Krieg. (Pp. xi + 299; 185 figures. 75*s*. 6*d*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1954.

The Diagnosis and Treatment of Convulsive Disorders in Children. By Samuel Livingston. (Pp. xx + 314; 71 figures. 69*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1954.

Clinical Psychiatry. By William Mayer-Gross, Eliot Slater, and Martin Roth. (Pp. xiii + 652; 16 plates. 50*s*.) London: Cassell. 1954.

The Spino-Cerebellar Degeneration. By J. G. Greenfield. (Pp. xi + 112. 17*s*. 6*d*.) Oxford: Blackwell Scientific Publications.

Aspects of Cerebellar Anatomy. Edited by Jan Jansen and Alf Brodal. (Pp. 423; 92 figures.) Oslo: Johan Grundt Tanum.

Wartime Psychiatry: A Compendium of the International Literature. Edited by Nolan D. C. Lewis and Bernice Engle. (Pp. vi + 952. 120*s*.) London: Oxford University Press (Geoffrey Cumberlege). 1954.

Graphologie et Physiologie de L'Écriture. By H. Callewaert. (Pp. 168; 30 plates. Fr.b. 90.–; $1.80.) Louvain: E. Nauwelaerts. 1954.

Abnormal Movements of the Face. By Samuel C. Little. (Pp. 70; 13 figures. $2.00.) Alabama: University of Alabama. 1954.

The Clinical Examination of the Nervous System. By G. H. Monrad-Krohn. (Pp. xx + 428; 165 figures. 36*s*.) London: H. K. Lewis. 1954.

Cerebrovascular Disease. By J. Peter Murphy; Foreword by Percival Bailey. (Pp. 408; 128 figures. 90*s*.; $12.00.) Chicago: The Year Book Publishers. 1954.

Röntgendiagnostik des Schädels. By Willy Loepp and Reinhold Lorenz. (Pp. xvi + 579; 613 figures. DM. 97.–.) Stuttgart: Georg Thieme Verlag. 1954.

The Lowenfeld Mosaic Test. By Margaret Lowenfeld. (Pp. 300; 144 colour plates. 50*s*.) London: Newman Neame. 1954.

The Study of the Brain. A Companion Text to the Stereoscopic Atlas of Neuroanatomy. By Hyman S. Rubinstein; Foreword by Carl L. Davis. (Pp. xiii + 209; 43 plates. $9.50.) New York: Grune & Stratton. 1953.

The Mental Hospital. By Alfred H. Stanton and Morris S. Schwartz. (Pp. xx + 492. $7.50.) New York: Basic Books. 1954.

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